A STUDY OF IRON-CATALYZED REDUCTIVE CYCLIZATIONS OF 1,6-DIENES, 1,6-ENYNES, 1,6-DIYNES: REACTIONS THAT PROCEED VIA METALLOCYCLIC INTERMEDIATES.

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Kevin Thomas Sylvester

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A STUDY OF IRON-CATALYZED REDUCTIVE CYCLIZATIONS OF 1,6-DIENES, 1,6-ENYNES, 1,6-DIYNES: REACTIONS THAT PROCEED VIA METALLOCYCLIC INTERMEDIATES.

Kevin Thomas Sylvester, Ph.D.

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A series of cyclization reactions catalyzed by (^{R}PDI)M(N_2)$_2$ (M = Fe, Co; ^{R}PDI = 2,6-(2',6'-R_2-C_6H_3N=CMe)$_2$$C_5H_3N$; R= iPr, Me; ^{trips}PDI = 2,6-(2',4',6'-$^{i}Pr_3$-C_6H_3N=CMe)$_2$$C_5H_3N$) was presented. The first reaction was a novel iron-catalyzed, hydrogen-mediated cyclization of 1,6-enynes and 1,6-diynes. This methodology employed mild conditions (room temperature and four atmospheres of hydrogen) and exhibited broad substrate scope. The reaction mechanism was studied through stoichiometric reactions and various deuterium labeling experiments, which revealed that transfer hydrogenation from the ligand isopropyl group was involved in the rate limiting step. This presents a rare example of bis(imino)pyridine ligands as both redox-active and chemically-active. The second reaction studied was an extension of the unprecedented iron-catalyzed [2π+2π] cyclization of unactivated 1,6-dienes to prepare [3.2.0]bicycloheptanes. The substrate scope was expanded and novel reactivity was observed. When a less sterically demanding ligand framework, ^{Me}PDI, and a less reducing catalyst, (^{iPr}PDI)Co(N_2), were used, a new product identified as an exomethylene-cyclopentane was observed. Higher temperatures favored the expected bicyclic product. The mechanism of the [2π+2π] cyclization was studied through a series of deuterium labeling experiments. It was determined through extensive deuterium scrambling that the reaction may be best described as a controlled radical reaction. The final study involved the preparation of relevant intermediates along the enyne and diyne cyclization. These iron-metallocyclopentanes were studied by

preparation of (^{R}PDI)Fe(biphenyl) and (^{R}PDI)Fe(diyne) (R = iPr, Me; (biphenyl = 2,2'-$C_{12}H_8$); diyne = bis(2-butynyl)tosylamine) complexes, which were analyzed by single crystal X-ray diffraction and Mössbauer spectroscopy. The electronic structure of these intermediates suggest that cycloaddition of dienes, eynes, or diynes results in a one-electron reduction of the bis(imino)pyridine ligand and one electron oxidation of the iron-center. In the case of the (^{R}PDI)Fe(biphenyl) and (^{R}PDI)Fe(diyne) complexes, these ferric centers have been assigned as low spin. However, for the intermediates of the related diene and enyne cyclizations, the ferric center could have a different spin state, thus accounting for their inability to be isolated.

BIOGRAPHICAL SKETCH

Kevin Sylvester was born in 1983 in northeast Philadelphia, Pennsylvania to Kenneth and Kathleen Sylvester. Promptly moving to the suburbs in the mid-eighties, he grew up in Churchville, PA. After attending grade school at Nativity of Our Lord in Warminster, PA, he graduated from Holy Ghost Prep in 2001. Following his childhood dreams to become a doctor, Kevin enrolled at Ursinus College in 2001 with a guaranteed seat at Drexel Medical School (starting in 2005). However, through forces beyond his control, he fell in love with organic chemistry. Under the direction of Dr. Ronald Hess, he did basic research in the area of ketene polymerization. After accepting a pair of summer internships in the pharmaceutical industry, he was lured away from biology into the sister science of chemistry and eventually decided to attend graduate school. Upon graduating *magna cum laude* with a B.S. in chemistry and a minor in biology, he embarked upon his grad school journey at Cornell University in the lovely small town of Ithaca, NY. Despite the best efforts of the cosmic forces, he was able to initially join the lab of Prof. Tyler McQuade and worked on solid supported catalysis and reactions in flow. Kevin then joined the lab of Prof. Paul Chirik. Charged with bringing some organic chemistry to the group, Kevin worked on iron-catalyzed cyclization reactions. Having some modest success in graduate school with organometallic chemistry, Kevin is currently employed as a post-doc in the laboratory of Abigail Doyle at Princeton University in hopes of honing his organic synthesis skills. Recently, he married his graduate school sweetheart, Emily C. Volpe in a beautiful wedding in picturesque Wheeling, WV. He is looking forward to the rest of his life with his lovely wife and hopes to find a job in the pharmaceutical industry or working for the government.

To my beloved parents: Kenneth and Kathleen Sylvester &

To my beautiful and patient wife, Emily (Volpe) Sylvester

ACKNOWLEDGMENTS

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learned to thoroughly analyze papers and data with which I am presented. This has made me become a better scientist with a more discerning eye.

I would also like to thank my boxmates throughout my tenure in the Chirik group; most especially, Don Knobloch for his mutual dislike of Reggae explosion and mutual love of Foreigner Friday (and later Weezer Wednesday and Styx Saturday). His synthetic skills were second to none and I enjoyed watching his group IV projects progress. Thanks for properly identifying the *cis*- and *trans*- isomers for my enyne/diyne cyclization. Also, I would like to mention Andrew(ski) Patrick for being from Texas (and all that implies…George Strait, Garth Brooks, etc.).

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CHAPTER 1

IRON-CATALYZED REDUCTIVE CYCLIZATION OF 1,6-ENYNES AND 1,6-DIYNES: EVIDENCE FOR PYRIDYL(DIIMINE) LIGAND INVOLVEMENT*

1.1 Abstract

(^{iPr}PDI)Fe(N_2)$_2$ (^{iPr}PDI = 2,6-(2',6'-$^{i}Pr_2$-C_6H_3N=CMe); 1-(N_2)$_2$) has been demonstrated to be both a competent catalyst for the hydrogenation of olefins and an efficient cyclization catalyst for the cycloisomerization of 1,6-dienes. Extending this chemistry to enyne and diyne substrates has resulted in a versatile iron-catalyzed, hydrogen-mediated method for the construction of various heterocycles under mild conditions. This methodology exhibits fairly broad substrate scope and excellent activities rivaling similar rhodium catalysts. This chapter will also explore the mechanism of this transformation. The reaction proceeds through an iron(II) metallocyclic intermediate which homolytically reacts with hydrogen to form the observed pyrrolidine (tetrahydrofuran or cyclopentane). The stoichiometric reaction was also studied and ligand involvement was observed via transfer-hydrogenation from the isopropyl methyl group to the iron(II) metallocycle. This iron-mediated process presents a rare example of PDI as being both redox and chemically non-innocent. The mechanism of the transfer hydrogenation was also studied, and this process was determined to be involved in the rate-limiting step.

1.2 Introduction

Heterocycles and other cyclic structures are a common motif in natural products and medicinal compounds. Methodologies to prepare these compounds with high

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chemoselectivity and high enantioselectivity from cheap and easily accessible intermediates are one common goal for organic chemists.[1] As synthetic methods have progressed, transition metals have begun to play a more integral role in the preparation of biologically active and medicinally relevant compounds. Transformations such as reductive cyclizations, olefin-metathesis, and hydroamination, are a few examples of methods employed to prepare natural product analogs that are typically catalyzed by noble metals such as platinum, rhodium, palladium, and ruthenium. However, the high price and scarcity of noble metals have allowed for the greater exploration and development of methods to supplant the use of noble metals with base metals such as cobalt, manganese, iron, and nickel.

A variety of reductive cyclization reactions are catalyzed or promoted by transition metals, especially group eight, nine, and ten transition metals. Typically, these reactions proceed via metallocyclic intermediates resulting from electrocyclization. These transient intermediates can be decomposed by numerous reagents (like hydrogen, carbon monoxide, and silanes) as well as by reductive elimination. The Pauson-Khand reaction (PKR) is a classic example of a reductive cyclization which proceeds through a metallocylic intermediate. The PKR involves the coupling of an olefin and an alkyne with carbon monoxide to synthesize cyclopentanone derivatives (Figure 1.1). Dicobalt octacarbonyl[2] was the first transition metal observed to promote this transformation under harsh conditions involving high temperatures, extended reaction times, and low yields.

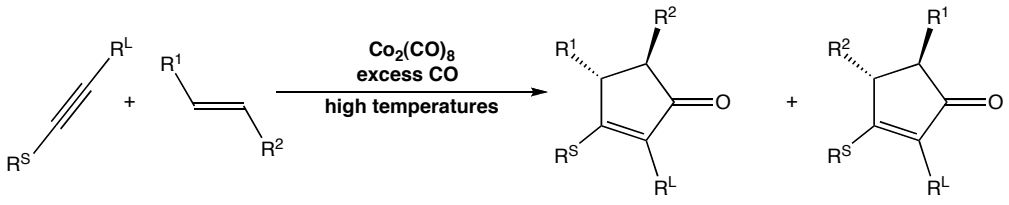
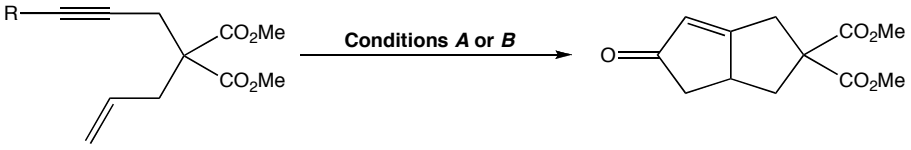


Figure 1.1. General Pauson-Khand reaction which proceeds through a metallocyclic intermediate.

The metal-mediated intermolecular PKR has been riddled with selectively issues; however, the metal-mediated intramolecular variant provided an efficient way to prepare bicyclic ketones.[3] Subsequently this method has been made catalytic when certain rhodium[4] or cobalt[5] complexes were employed to prepare bicyclic ketones in good yield (Figure 1.2). An enantioselective version of the PKR was reported when $Rh(cod)BPh_4$ and BINAP were employed as the catalyst system resulting in high yields and good enatiomeric excesses. The PKR represents an early example of reductive cyclization, which was reported to proceed through a metallocyclic intermediate.



A (R=H): 3 mol % $Co_2(CO)_6[(PhO)_3P]_2$, 3 atm CO, dme, 110 °C, 24 h, 80 % yield
B (R=Me): 5 mol % $(Ph_3P)_3RhCl$, 10 mol % AgOTf, 1 atm CO, toluene, 110 °C, 18 h, 78 % yield

Figure 1.2. Catalytic Pauson-Khand reaction using group nine transition metals.

Reductive cyclizations of enynes employing palladium have ample precedent in the literature. With various palladium(II) precursors as catalysts supported by phosphine ligands, and carboxylic acids as proton sources, enynes can be cleanly converted to exo-methylene cyclopentane derivatives. One example, developed by Trost and coworkers, invoked a palladium alkyl that is susceptible to reduction by the presence of a Si-H bond (Figure 1.3).[6]

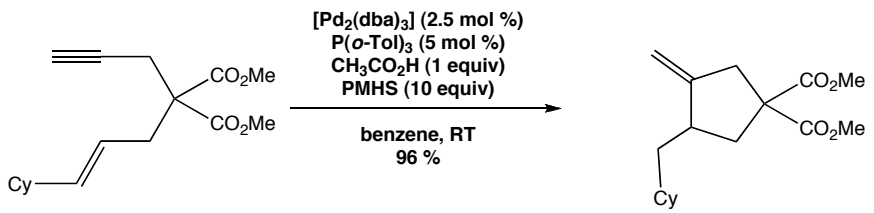


Figure 1.3. Reductive cyclization catalyzed by palladium with silane as hydrogen source.

Rhodium compounds have also been employed as catalysts to prepare ring structures of various sizes. One example by Wender[7] and coworkers allows for the facile formation of [5.3.0]bicyclodecane derivatives via [5+2] cycloadditons from cyclopropyl-enynes (Figure 1.4). These products were formed in good yield by accessing a rhodium(II) metallocycle which inserted the cyclopropyl moeity, and subsequent reductive elimination furnished the observed bicyclic product.

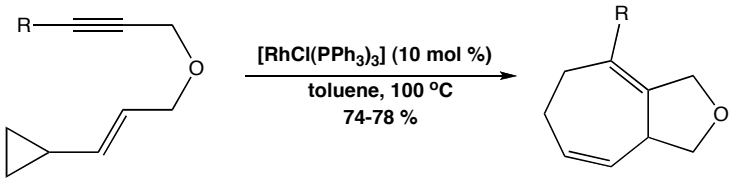


Figure 1.4. Ring expansion reaction catalyzed by rhodium.

Moreover, in the presence of rhodium catalysts, various enynes underwent reductive cyclization with either silanes or elemental hydrogen as the stoichiometric reductant. Ojima[8] reported dimethylphenyl silane as a trap for the proposed metallocyclic intermediate resulting from the electrocyclization of the rhodium center with the enyne (Figure 1.5). The yields for this transformation were good to excellent under fairly mild conditions. Similarly, Widenhoefer[9] and coworkers reported the enantioselective version of this cyclization using $[Rh(cod)_2]PF_6$ as a catayst in the presence of a chiral bis-phosphine and triethylsilane. Good to excellent yields were observed along with high enantioselectivities.

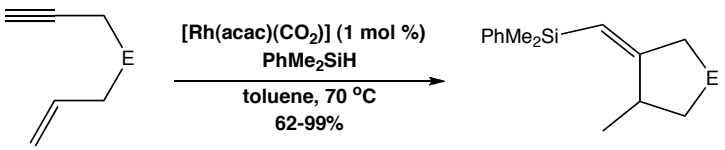


Figure 1.5. Rhodium-catalyzed, silane-mediated reductive cyclization.

Like other group ten congeners, low-valent nickel catalyzes an array of cyclization reactions. Low valent nickel is typically accessed using nickel bis(cyclooctadiene) or by in situ reduction of nickel(II) salts. One example[10] (Figure 1.6) involves the in situ reduction of $Ni(acac)_2$ with diisopropyl zinc to access Ni^0. Nickel then intercepts one equivalent of enyne substrate resulting in the formation of a nickelmetallocyclopentane.

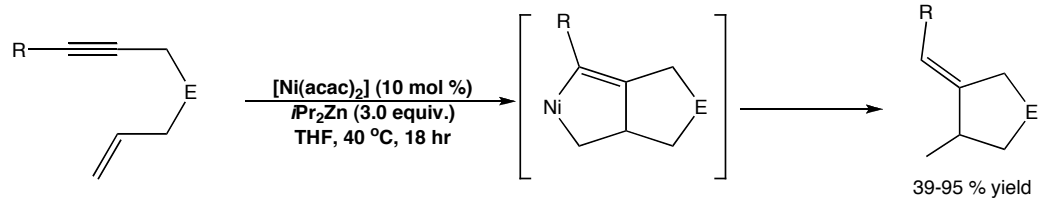


Figure 1.6. Nickel-catalyzed reductive cyclization of enynes mediated by dialkyl zinc.

Subsequent transmetallation with diisopropylzinc results in the formation of two distinct intermediates (Figure 1.7), both nickel dialkyls. β-hydrogen elimination of the Ni-isopropyl fragment yields a nickel hydride, which upon reductive elimination and hydrolysis yields the expected cyclic product. This methodology produced pyrrolidines and tetrahydrofurans in moderate to good yields with excellent Z:E selectivity (99:1).

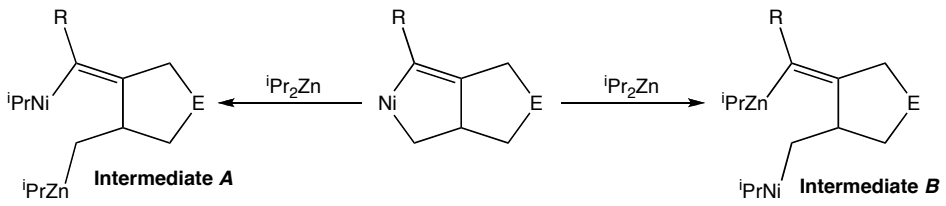


Figure 1.7. Proposed mechanism for the decomposition of Ni-metallocycle.

Oshima and coworkers reported the manganese-mediated cyclization of diynes and enyes to form azobicyclo[5.3.0]deca-dienes.[11] The preparation of these products suffered from low to moderate yields and mixtures of products. However, the invoked intermediate in this stoichimetric process is a bicyclic manganacyclopentadiene (Figure 1.8), which upon hydrolysis liberated the pyrrolidine (in 40 % yield when $R^1 = R^2 = PhC{\equiv}CCH_2$). This experiment is consistent with the proposed intermediate, and insertion of the pendant allyl group would account for the observed bicyclic products. When this methodology was extended to enynes, the observed product was an exo-methylene pyrrolidine.

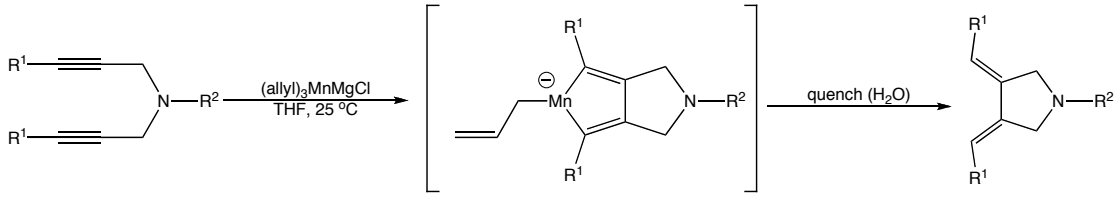


Figure 1.8. Manganese-mediated diyne cyclization.

Rhodium-catalyzed, hydrogen-mediated enantioselective cyclizations have recently been reported by Krische and coworkers[12] (Figure 1.9). This reaction has excellent substrate scope and enantiomeric excess values, with many greater than 90%. The reaction is thought to proceed via the heterolytic cleavage of hydrogen because an external base is required in the catalytic cycle. Specfically, triflate acts as a

base and forms a rhodium hydride, which is thought to be the active species. This methodology has been described as "green," as a result of the exceptional atom economy and the mild conditions. However, relatively high catalyst loadings of expensive rhodium and the employment of dichloroethane as the reaction solvent significantly diminish the green implications for this methodology.

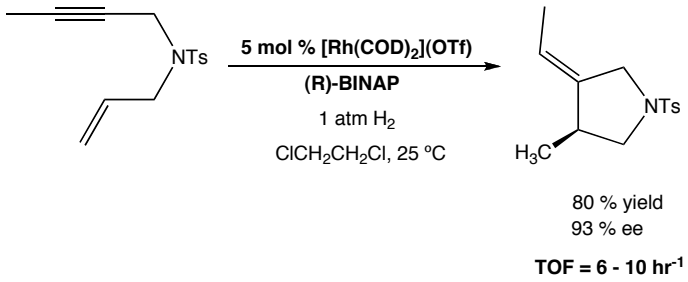


Figure 1.9. Rhodium-catalyzed, hydrogen-mediated reductive cyclization.

The main focus of the Chirik group is to elucidate the electronic structure of various iron compounds and then employ this understanding to rationalize mechanisms and to develop catalytic reactions. One of the main complexes that has found application in catalysis is (^{iPr}PDI)Fe(N_2)$_2$, a proven hydrogenation catalyst[13] and isomerization catalyst[14] of olefins and alkynes (Figure 1.10). The former transformation enjoys broad substrate scope, as well as excellent turnover frequencies (>240 hr^{-1} for some substrates) which rival precious metals such as Wilkinson's catalyst[15]. Additionally, (^{iPr}PDI)Fe(N_2)$_2$ catalyzes the facile isomerization of 1,6-dienes to [3.2.0]bicycloheptanes. This transformation is unique because it is thermal and does not require light to occur. Furthermore, it is one of the few examples of cyclobutane formation under fairly mild conditions (room temperature, 5 mol % catalyst, and reaction time less than five hours). The explanation for this reactivity lies in the fact that the PDI ligand itself can accept and give electrons, allowing the iron center to remain in a stable Fe(II) oxidation state (Figure 1.11). It is based on these

two abilities of (^{iPr}PDI)Fe(N_2)$_2$ that the hydrogenative cyclization of enynes and diynes was developed. This chapter will discuss the scope and mechanism of the reaction. Moreover, the stoichiometric reaction between (^{iPr}PDI)Fe(N_2)$_2$ and enynes or diynes will also be analyzed, including the mechanism and some labeling studies to highlight the importance of metallocyclic intermediates in many transition metal-catalyzed reactions.

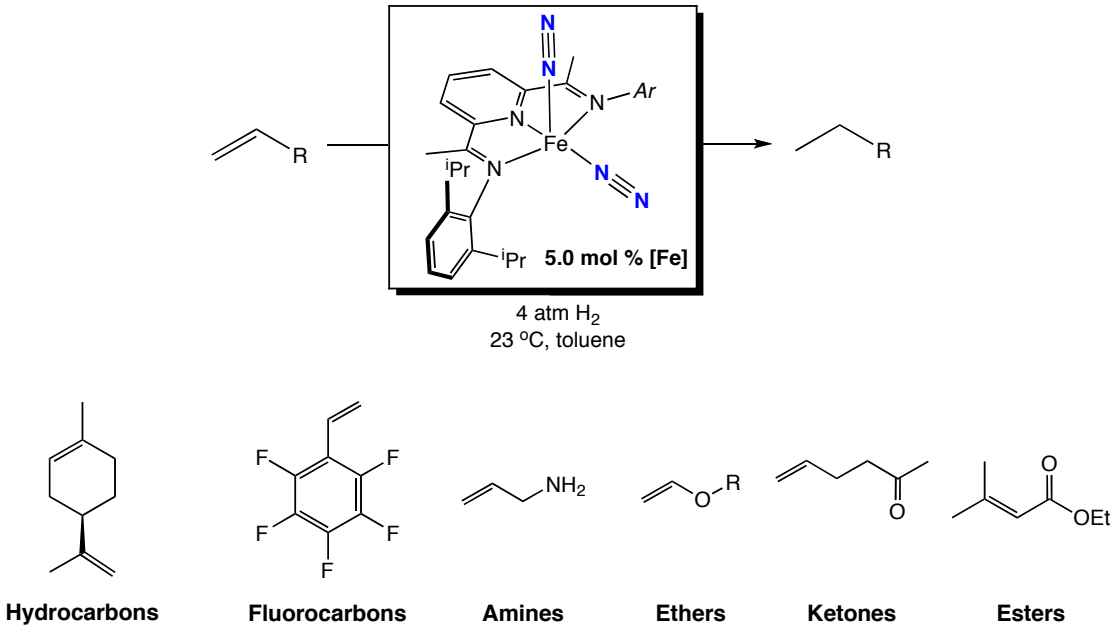


Figure 1.10. Hydrogenation of olefins using (^{iPr}PDI)Fe(N_2)$_2$.

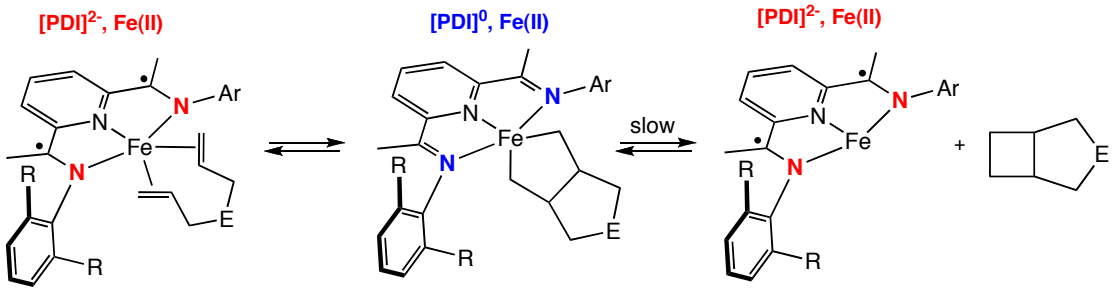


Figure 1.11. Cyclization reaction of unactivated 1,6-dienes catalyzed by (^{iPr}PDI)Fe(N_2)$_2$.

1.3 Results

Stoichiometric Reactions with Enynes. When allyl-2-butynyl tosylamine was exposed to one equivalent (^{iPr}PDI)Fe(N_2)$_2$, the reaction immediately turned from green to red. ^{1}H-NMR analysis of the red solution revealed consumption of both starting materials and the formation of a paramagnetic compound. After three hours, the solution turned brown and all of the paramagnetic resonances disappeared, giving way to a diamagnetic product (the organic fragment); however, there was no evidence of a (PDI)Fe-containing species. Aqueous degradation of the brown solution and analysis of the resulting product revealed the formation of dehydrogenated ^{iPr}PDI as well as the tosyl pyrrolidine. This reaction was repeated with a series of other allyl-2-butynyl enyne substrates. In all cases, complete consumption of the starting materials was noted, immediately giving way to a red paramagnetic product. After about three hours the solution turned brown, revealing the NMR-silent olefin compound and the cyclopentyl product (Figure 1.12).

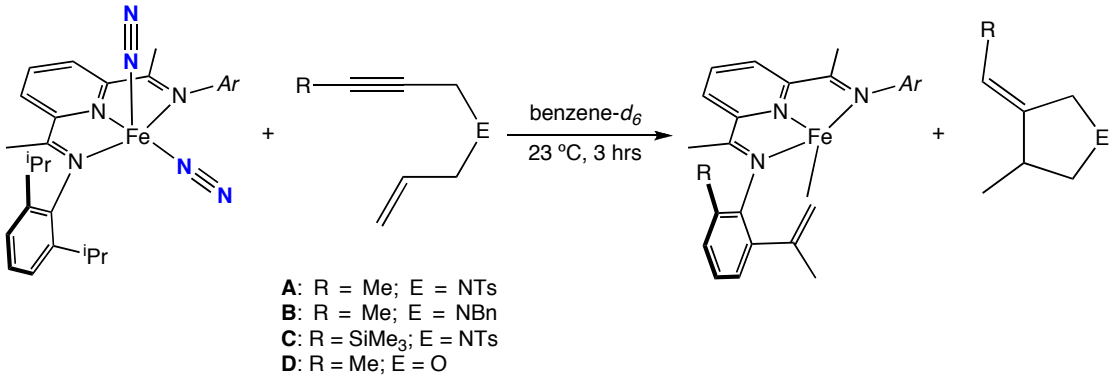


Figure 1.12. Stoichiometric reaction of enynes and (^{iPr}PDI)Fe(N_2)$_2$.

Stoichiometric Reactions with Diynes. With the successful conversion of enynes to the reduced cyclopentyl derivatives, diynes were next explored. Bis(2-butynyl)tosylamine was chosen as a model substrate. Combining this diyne with one

equivalent of (^{iPr}PDI)Fe(N_2)$_2$ resulted in consumption of both starting materials and the formation of a green-purple paramagnetic compound. Monitoring the reaction for eight hours resulted in the disappearance of the paramagnetic NMR signals and the formation of a diamagnetic product. Again, there was no evidence for a (PDI)Fe-containing species. Aqueous degradation of the brown reaction mixture and analysis by ^{1}H-NMR revealed formation of the dehydrogenated ligand and bis(exo-olefinic)pyrrolidine. This methodology was extended to a series of diynes. In all cases, complete consumption of the diyne was observed immediately, and after about eight hours a new diamagnetic product had formed, which was identified as the bis(exo-olefinic)cyclopentyl derivative. The other product that formed was the NMR-silent olefin compound, which was identified after degradation (Figure 1.13).

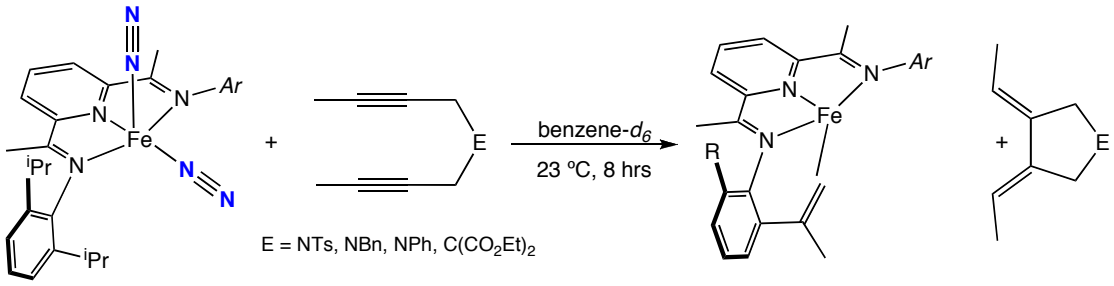


Figure 1.13. Stoichiometric reaction between diynes and (^{iPr}PDI)Fe(N_2)$_2$.

Stoichiometric Reactions with Labeled Ligand. The isopropyl methyl groups of (^{iPr}PDI)Fe(N_2)$_2$ can be easily labeled under deuterium in about twenty-four hours. This deuterated compound was employed to track the fate of the hydrogen transferred from the ligand to the enyne substrate. Combining one equivalent of allyl-2-butynyltosylamine with (^{iPr}PDI*)Fe(N_2)$_2$ (^{iPr}PDI* = d_{24}) led to the formation of a paramagnetic compound. The lifetime of this compound was 588 minutes. When the proteo reaction was monitored more carefully, complete consumption of the

metallocycle complex took 102 minutes. This ratio when calculated is approximately 6 ($k_H/k_D = 5.8$). When the labeled product was analzyed, the ratio of d_1-isomers was determined to be 3.5 to 1 where the major isomer had deuterium in the exo-methyl position (Figure 1.14).

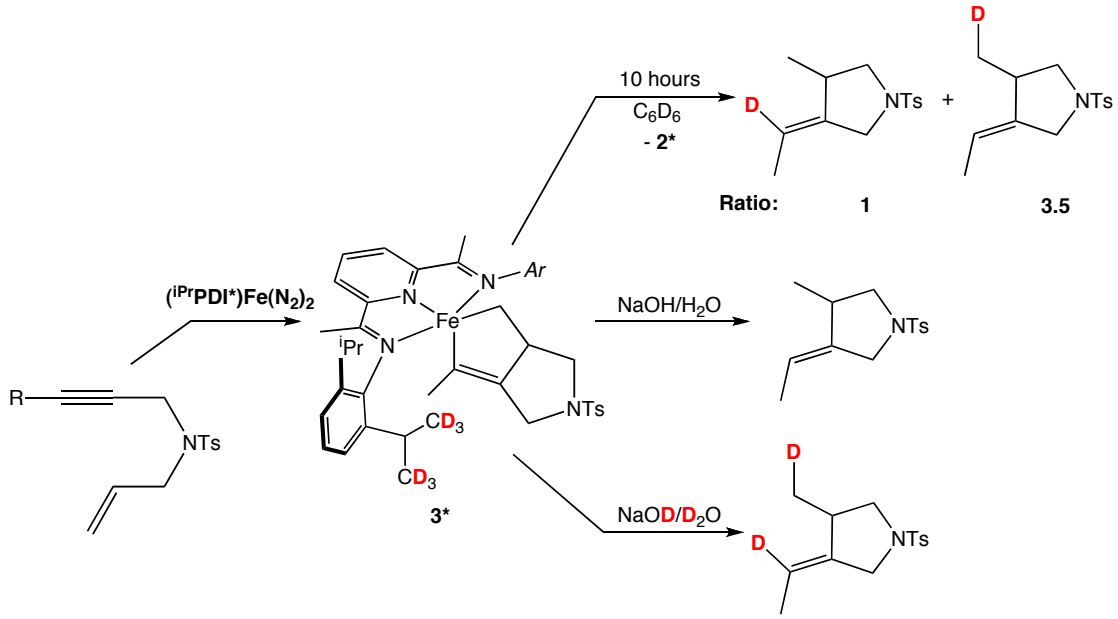


Figure 1.14. Reactions involving deuterium labeled metallocycle.

The kinetics of the transfer hydrogenation were also studied. The nitrogen compound was combined with the enyne. Addition of iodine at certain points caused decompsition of the metallocycle to free enyne and free ligand. As a result, conversion could be measured as a function of time. When unlabeled metallocycle decomposition was measured as a function of time, the rate constant was determined to be 6.6×10^{-4} $M^{-1}s^{-1}$ and for the labeled case, the rate constant was determined to be 1.1×10^{-4} $M^{-1}s^{-1}$, which is consistent with the aforementioned results.

Degradation studies on the metallocyclic intermediate were also done (Figure 1.15). When the labeled metallocycle was decomposed with water and base, the

proteo-pyrrolidine (with free ligand) was the observed organic product. Similarly, when the deuterated metallocycle was decomposed with deuterium oxide and NaOD, the resultant products were determined to be the d_2-pyrrolidine and free ligand. Finally, when the unlabeled metallocycle was decomposed with deuterium oxide and NaOD, the d_2-pyrrolidine was the isolated organic fragment. The identities of each of these products were determined by mass spectrometry and NMR (^{1}H, ^{2}H).

Catalytic reduction of enynes. When stoichiometric reactions between (^{iPr}PDI)Fe(N_2)$_2$ and enynes were run, the resulting iron product was the dehydrogenated-olefin compound. It was reasoned that the use of a stoichiometric source of hydrogen might allow for catalytic development of this reaction sequence.

As a test case, twenty equivalents of allyl-2-butynyltosylamine were combined with (^{iPr}PDI)Fe(N_2)$_2$ under four atmospheres of hydrogen. After three hours, the reaction was quenched. Analysis of the product mixture revealed complete consumption of the starting enyne. The enyne was completely converted to exo-alkenyl tosylpyrrolidine. This reaction was extended to other internal enynes. Facile conversion was observed for allyl-2-butynyl ether, allyl-2-butynylbenzylamine, and TMS-protected allylpropargyltosylamine. The yields for these four substrates ranged between 62 and 82 %.

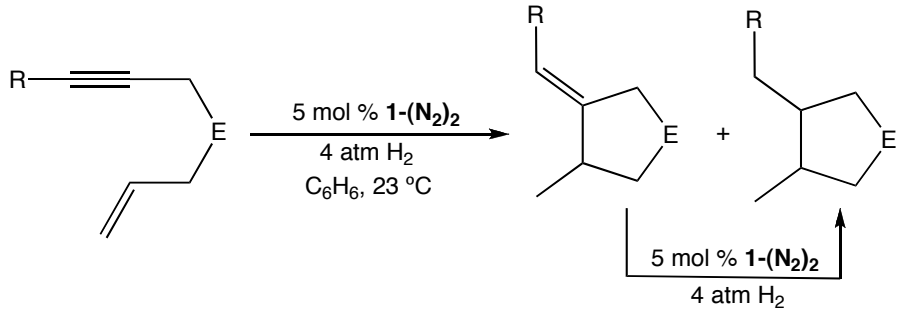
The next class of substrates studied was terminal enynes. Twenty equivalents of allyl propargyltosylamine were combined with (^{iPr}PDI)Fe(N_2)$_2$ in toluene and frozen. To the frozen solution, four atmospheres of hydrogen were added and the reaction was thawed. After sixty minutes, the reaction was quenched. Analysis of the reaction mixture revealed that the starting enyne was completely consumed. When the resulting product was analyzed by ^{1}H-NMR and GC-MS, the identity of the product was determined to be the bis(exo-methyl)tosylpyrrolidine. The ratio of inseparable

diastereomers was 3:1, with the major product being the *cis*-isomer, and the isolated yield was 79 %. With this successful reaction in hand, the scope of the reaction was studied. When the reaction was run for shorter periods of time and under a lower hydrogen pressure, the exo-methylene pyrrolidine was observed; dimethylpyrrolidine presumably resulted from the further hydrogenation of the exo-methylene pyrrolidine.

Other protected amino-enynes (benzyl, *t*-butyl) were completely consumed under four atmospheres of hydrogen with complete selectivity for the *cis*-isomer. When allyl propargyl(pentamethylbenzyl)amine was subjected to the standard reaction conditions, only 57% conversion to the dimethyl pyrrolidine was observed, along with 16 % conversion to the completely reduced amine. Again, the selectivity was complete for the *cis*-isomer.

When twenty equivalents of diethyl allyl propargyl malonate were exposed to four atmospheres of hydrogen and (^{iPr}PDI)Fe(N_2)$_2$, complete consumption of the enyne was observed with only 74 % conversion to the dimethyl cyclopentane and 26 % conversion to the completely reduced alkane. The ratio of *cis*- to *trans*- isomers was 79 to 21 with the *cis*-isomer as the major product. The final terminal enyne employed was allyl propargyl ether. The substrate underwent complete reductive cyclization to form the 3-methylene-4-methyl-tetrahydrofuran in six hours. When the reaction time was extended to 24 hours, dimethyl tetrahydrofuran was formed in about 53 % conversion. A summary of results for each of the enyne substrates is presented in Table 1.1.

Table 1.1. Results of reductive cyclization of enynes.



	E	R	Time (min)	Yield[b] (%)	TOF[c] (hr^{-1})	*Cis*:*Trans* (Saturated)
1	N^tBu	H	180	68	6.7	> 99:1
2	NTs	H	60	79	20.0	75:25
3	NBn	H	180	71	6.7	> 99:1
4	$NCH_2C_6Me_5$	H	180	57[d]	4.9	> 99:1
5	NTs	Me	180	79	6.7	----
6	NBn	Me	180	71	6.7	----
7	NTs	$SiMe_3$	540	82	2.2	----
8	O	H	360	95	3.3	61:39[f]
9	O	Me	180	62	6.7	----
10	$(EtCO_2)_2C$	H	180	74[e]	6.7	79:21

a) Conditions: 4 atm of H_2 at 23 ºC. b) Isolated yield. c) Determined at > 95% conversion by ^{1}H-NMR spectroscopy and 99% GC-MS. d) 16 % reduced alkyne compound observed. e) 26 % reduced alkyne complex observed. f) 24 hrs, 53 % conversion to the 3,4-dimethyl-tetrahydrofuran.

Catalytic reductive cyclizations of diynes. Employing the standard conditions for the reduction of enynes with diynes, several substrates were tested (Figure 1.15). Bis(2-butynyl) tosylamine was exposed to 5 mol % (^{iPr}PDI)Fe(N_2)$_2$, and after a few hours complete conversion to the bis(exo-olefinic) tosylpyrrolidine was observed. Similarly, bis(2-butynyl) benzylamine underwent clean conversion to the bis(exo-olefinic) amine. However, in the case of bis(2-butynyl) aniline and bis(2-butynyl) diethylmalonate, significant amounts of completely reduced alkyne were observed. For the aniline, the resulting product could be separated by washing the reaction

mixture with cold pentane, whereas in the case of the malonate, the reduced alkyne and the cyclized product could not be separated.

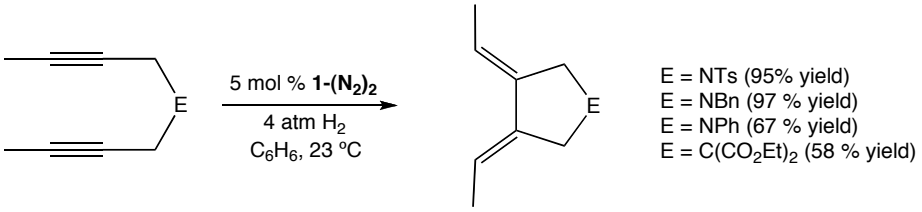


Figure 1.15. Reduction of alkynes using hydrogen and (^{iPr}PDI)Fe(N_2)$_2$.

Catalytic hydrogenation using deuterium gas. To probe the mechanism of the hydrogenation, deuterium gas was employed as a marker to determine the fate the hydrogen in the reaction (Figure 1.16). Allyl-2-butynyl tosylamine (twenty equivalents) was subjected to (^{iPr}PDI)Fe(N_2)$_2$ under four atmospheres of deuterium gas. After eight hours, the reaction was quenched and the resulting organic product was determined to be exo-olefinic tosylpyrrolidine with exclusive deuterium incorporation in the exo-methine and the exo-methyl group. Careful analysis of the deuterium NMR spectrum of the reaction mixture also revealed that deuterium incorporation into the ligand only occurred in the isopropyl methyl groups (and not into the methine position). Similarly, bis(2-butynyl) tosylamine, when exposed to the same reaction conditions, resulted in the formation of bis(olefinic) pyrrolidine that exhibited exclusive deuterium incorporation into the vinylic positions. Allyl propargyl tosylamine was also exposed to 5 mol % catalyst under four atmospheres of deuterium. The isolated product was the d_4-dimethyl pyrrolidine that showed incorporation into the exo-methyl positions as well as the methine of the pyrrolidine ring. The d_4-isotopomer resulted from continued deuteration of the exo-methyelene pyrrolidine produced from the addition of one equivalent of deuterium to the metallocyclic intermediate.

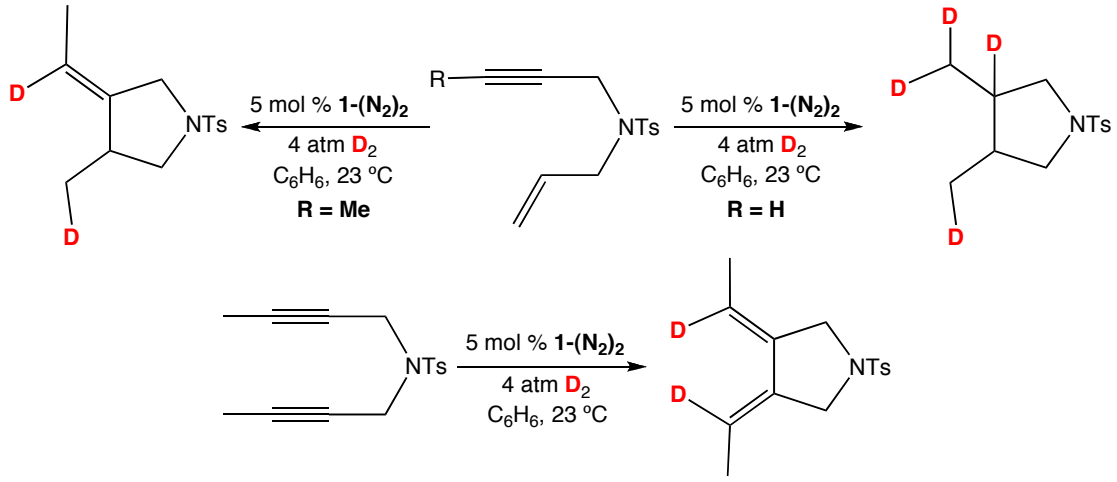


Figure 1.16. Results of iron-catalyzed cyclizations under deuterium.

Reductive cyclization using phenylsilane as a reductant. Phenylsilane was employed as a stoichiometric reductant. It was found that this reaction sequence allows for the clean hydrogenation and isolation of a variety of tosyl-protected amino-enynes (Figure 1.17). Good to moderate yields were obtained with the three substrates tested.

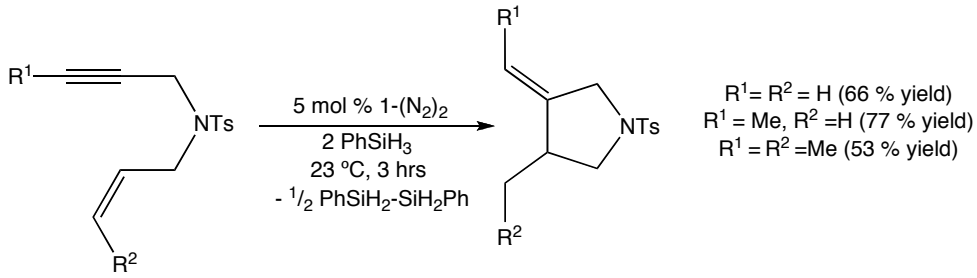
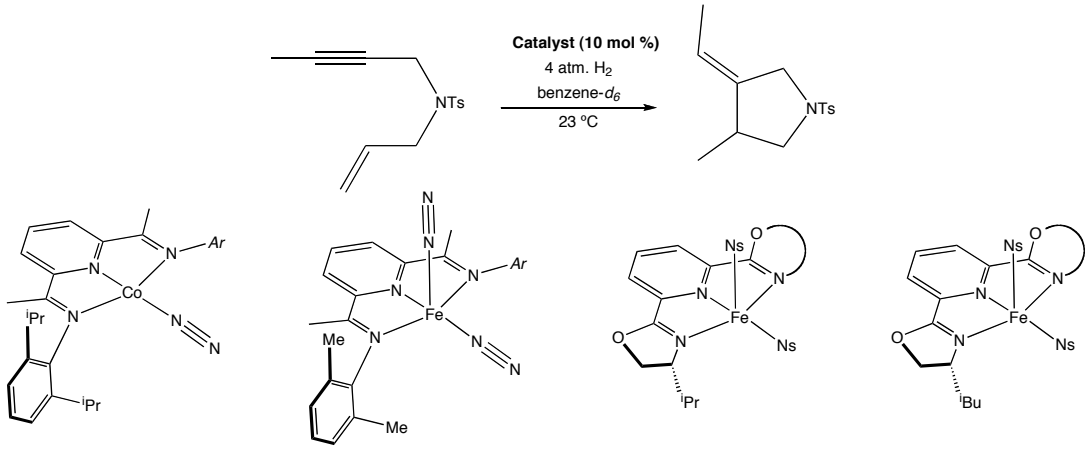


Figure 1.17. Reductive cyclization of tosyl aminoenynes using phenylsilane.

Reductive cyclizations catalyzed by other base metal catalysts. Other base metal catalysts were subjected to the same reaction conditions (four atmospheres hydrogen). When (^{iPr}PDI)Co(N_2)$_2$ and [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) were separately combined with ten equivalents of allyl 2-butynyl tosylamine under hydrogen, complete consumption

of substrate was observed. For the cobalt catalyst, eight hours were required for the reaction to reach completion, whereas the (^{Me}PDI)Fe catalyst required only three hours to completely convert the enyne to the pyrrolidine. There was no expected enantiomeric excess because the ligand set was not chiral.

However, when chiral iron-pybox compounds were employed, some degree of enantioselectivity was anticipated. Hydrogen was effective for the activation of the iron dialkyl catalysts as evidenced by a color change from a dark violet solution to a brownish green solution. After twelve hours, (^{iPr}pybox)FeNs$_2$ (Ns = neosilyl) (5 mol %) completely converted the enyne to the pyrrolidine, but showed poor enantiomeric excess (e.e.) when the reaction was analyzed by chiral GC-MS. A similar result was observed when (^{iBu}pybox)FeNs$_2$ was employed as the catalyst, but only 72 % conversion was observed after 16 hours and the e.e. was measured to be 10 % (Figure 1.18). Pybox iron dialkyls are effective catalysts for the preparation of pyrrolidines via reductive cyclization, but lack the capacity to induce enantioselectivity.



% Conversion	**>95 %**	**>95%**	**>95 %**	**72 %**
Enantiomeric Excess	**N/A**	**N/A**	**~5%**	**~10%**

Figure 1.18. Enyne reductive cyclization results with catalyst variants.

1.4 Discussion

In this chapter, a method for the catalytic hydrogenative cyclization of enynes and diynes was developed. This transformation is of interest because a base metal has been employed to prepare biologically and pharmaceutically relevant chemical motifs using hydrogen as the stoichiometric and perfectly atom-economic reductant.

The substrate scope of this methodology is fairly robust, tolerating protected amines, esters, and ethers. The substrate scope is noteworthy for a few reasons. Previously attempted [2π+2π] cycloisomerizations with (^{iPr}PDI)Fe(N_2)$_2$ resulted in the detrimental cleavage of diallyl ether. Hence, the reductive cyclizations of allyl propargyl ether and allyl 2-butynyl ether in the presence of hydrogen are the first examples of successful ether cyclizations involving (^{iPr}PDI)Fe(N_2)$_2$. Moreover, this reaction methodology was amenable to substitution on the alkyne, whereas for the cycloisomerization of 1,6-dienes by (^{iPr}PDI)Fe(N_2)$_2$, di-α-olefins were the only substrates that were easily converted to the [3.2.0]bicycloheptane motif.

Despite the successful implementation of this methodology, there were a few problems. (^{iPr}PDI)Fe(N_2)$_2$ is a very competent hydrogenation catalyst with activity that rivals precious metals such as rhodium. Thus, for some of the enynes and diyne substrates, a significant portion of completely saturated compound (i.e., linear alkane product) was observed. Since – as a result of transfer hydrogenation from the isopropyl group – the reaction yields the product with or without hydrogen, then theoretically it could be optimized with the appropriate pressure of hydrogen for each substrate. Moreover, when terminal enynes were employed, the isolated product was the dimethyl cyclopentane (tetrahydrofuran or pyrrolidine). This resulted from the hydrogenation of geminal exo-alkene that was formed in the initial cyclization and hydrogenation. One prospect of better control of the hydrogenation is the use of a different hydrogen source. This was only moderately explored by the employment of

phenylsilane as a hydrogen source. As this reaction was successful for the few substrates for which it was tested, it may present a viable alternative to the use of hydrogen for substrates that are easily reduced.

Stoichiometric reactions of enynes and diynes with (^{iPr}PDI)Fe(N_2)$_2$ resulted in transfer hydrogenation from the ligand to form the pyrrolidine. This reaction was studied with the aid of labeling. For the metallocycle with the labels in the isopropyl groups, degradation with proteo-water and NaOH indicated that the there were two iron-carbon bonds present; lack of deuterium incorporation into the pyrrolidine implied that release of the organic fragment occurred by protonation. Also, the ligand remained intact. (Minimal or no dehydrogenation was noted.) When deuterium oxide was used to degrade the labeled metallocycle, the d_2-pyrrolidine formation and unmodified ligand indicated that the protonation occurred as a result of the water and not transfer from the ligand. These results are consistent with the formation of the proposed metallocyclic intermediate followed by protonation of the iron-carbon bonds.

The mechanism of this reaction was explored using deuterium gas. The most telling experiment was the cyclization of allyl 2-butynyl tosylamine under deuterium, which resulted in the formation of the tosylated d_2-pyrrolidine. This reaction indicated that the proposed metallocyclic intermediate is cleaved by one equivalent of deuterium. The exact mechanism will be discussed in greater detail later. However, the incorporation of deuterium into only the isopropyl methyl groups of the ligand indicated that it is not directly involved in the catalytic reaction. If the ligand had been involved in the mechanism, deuterium incorporation into the isopropyl methine should have been observed, since the olefin compound that is formed in the stoichiometric reaction can be hydrogenated to form the active catalyst.

Allyl propargyl tosylamine was completely converted to the tosyl d_4-pyrrolidine because the first equivalent of deuterium was added across the metal carbon bonds of the metallocycle, releasing the exo-alkenyl d_2-pyrrolidine. The pyrrolidine would subsequently undergo further reduction under the influence of (^{iPr}PDI)Fe and deuterium. When twenty equivalents bis(2-butynyl) tosylamine were exposed to (^{iPr}PDI)Fe$(N_2)_2$ and deuterium, the expected d_2-pyrrolidine was isolated. This reaction was consistent with the labeling experiments, and the bis-olefinic pyrrolidine was observed because of the inability of (^{iPr}PDI)Fe$(N_2)_2$ to hydrogenate trisubstituted alkenes.

The hydrogenation of the enynes was thought to proceed through the metallocycle, which was believed to be iron(II) (Figure 1.19). After the initial cyclization reaction to form the bimetallocycle, hydrogen would break the two metal-carbon bonds. However, the exact process by which the hydrogenation occurs is not clear. In one case, a simple sigma bond methathesis could occur between one molecule of dihydrogen and the metallocycle. If this mechanism were operating, the metathesis could occur at either the iron-alkyl bond or the iron-alkenyl bond, but mechanistically, these two events cannot be distinguished. It seems more likely that the iron-alkyl bond is broken first, because it is the weaker metal carbon bond and the resulting iron alkenyl hydride should be a more stable intermediate. An alternate mechanism is the oxidative addition of hydrogen to the iron center, resulting in a potentially seven-coordinate intermediate with an iron center in the +4 oxidation state. Iron(IV) has been proposed as an intermediate in the hydrogenation work done by Peters and coworkers[16], so it is not unreasonable to suggest it as an intermediate in this instance. However, the Peters' intermediate is a trihydride. The suggested mechanism for the iron-catalyzed reductive cyclization differs from the rhodium variant that was developed by Krische. In the work done by Krsiche, the reaction proceeds via the

heterolytic cleavage of hydrogen. The requirement for an external base (i.e., triflate) supports this mechanism.

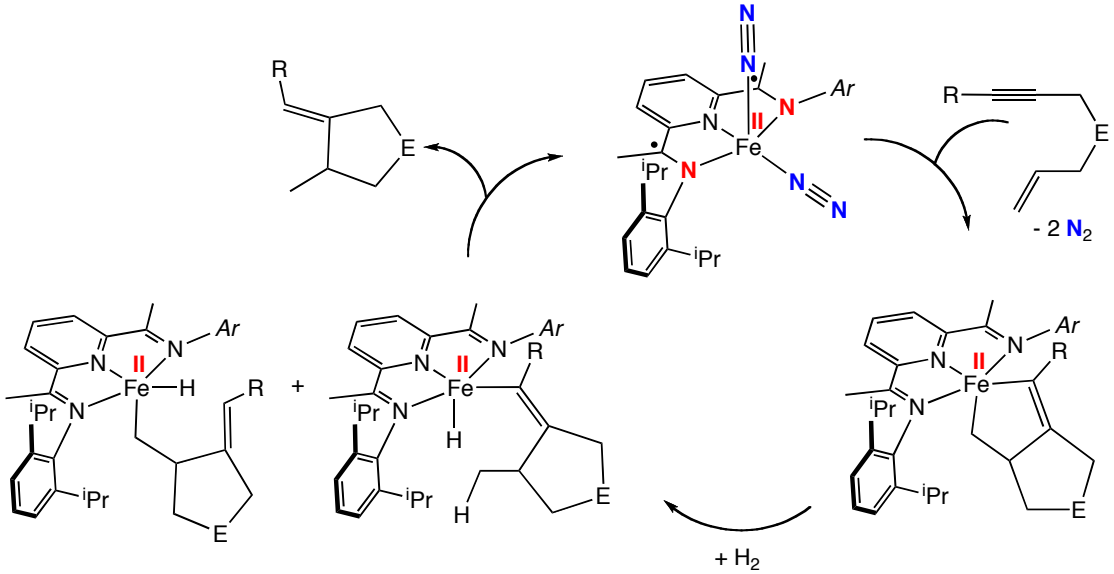


Figure 1.19. Proposed mechanism for catalytic hydrogenation of enynes using reduced iron compounds.

Despite the feasibility of the previously presented mechanism (homolytic cleavage of hydrogen by an iron(II) intermediate), recent work has indicated that the oxidation state of the intermediate metallocycle may in fact be iron(III). This conclusion comes from Mössbauer as well as crystallographic data. This will be further explored in chapter three with the study of the oxidation of biphenylene to reduced iron centers and the subsequent chemistry that the resulting compounds undergo.

1.5 Conclusion.

Iron catalysts can perform the role of more expensive precious metals. The utility of (^{iPr}PDI)Fe(N_2)$_2$ as a rhodium surrogate has been clearly demonstrated in the hydrogen-mediated reductive cyclizations of 1,6-enynes and 1,6-diynes, because the substrate scope and catalytic activities are similar to rhodium systems. The mechanism

of this transformation was explored through deuterium labeling. As a result of the catalytic deuteration, the proposed metallocycle is a reasonable intermediate because of exclusive deuterium corporation into the expected positions. Stoichiometric reactions between (^{iPr}PDI)Fe(N_2)$_2$ and enyne or diyne substrates indicate ligand involvement via transfer hydrogenation from the isopropyl methyl group. A kinetic isotope effect of ~6 was measured when comparing the transfer hydrogenation and transfer deuteration, which is consistent with the atom transfer being the rate-limiting step. The intermediate metallocycles were purported to be iron(II) based on previous assumptions about the redox-activity of the (PDI)Fe system; however, some more recent work may suggest that the intermediate may be iron(III). This will be further explored in chapter three.

1.6 Experimental Procedures.

General Considerations. All air- and moisture-sensitive manipulations were carried out using standard vacuum line, Schlenk and cannula techniques or in an MBraun inert atmosphere drybox containing an atmosphere of purified nitrogen. The MBraun drybox was equipped with a cold well designed for freezing samples in liquid nitrogen. Solvents for air- and moisture-sensitive manipulations were initially dried and deoxygenated using literature procedures.[17] Argon and dihydrogen gas were purchased from Airgas Incorporated and passed through a column containing manganese oxide supported on vermiculite and 4 Å molecular sieves before admission to the high vacuum line. Benzene-d_6 was purchased from Cambridge Isotope Laboratories and distilled from sodium metal under an atmosphere of argon and stored over 4 Å molecular sieves or sodium metal. $CDCl_3$ was purchased from Cambridge Isotope Laboratories and used as received. The metal complexes (^{iPr}PDI)Fe(N_2)$_2$,[18] (^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) ,[19] (^{iPr}PDI)Co(N_2),[20] (^{iPr}pybox)FeNs$_2$,[21] and (^{iBu}pybox)FeNs$_2$[21]

were prepared according to literature procedures. (^{trips}PDI)Fe(N_2)$_2$ was prepared in an analogous way to (^{iPr}PDI)Fe(N_2)$_2$.

^{1}H NMR spectra were recorded on Varian Mercury 300, Inova 400 and 500 spectrometers operating at 299.763, 399.780 and 500.62 MHz, respectively. All chemical shifts are reported relative to $SiMe_4$ using ^{1}H (residual) chemical shifts of the solvent as a secondary standard. For paramagnetic molecules, the ^{1}H NMR data are reported with the chemical shift followed by the peak width at half height in Hertz or multiplicity, followed by integration value and where possible, peak assignment.

Mass spectra were acquired using a JEOL GCMate II mass spectrometer operating at 500 (LRMS) or 3000 (HRMS) resolving power (20% FWHM) in positive ion mode and an electron ionization (EI) potential of 70 eV. Samples were introduced via a GC inlet using an Agilent HP 6890N GC equipped with a 30 m (0.25 μ i.d.) HP-5ms capillary GC column. The carrier gas is helium with a flow rate of 1 mL/min. Samples were introduced into the GC using a split/splitless injector at 230 ˚C with a split ratio of 10:1 (HRMS) or 50:1 (LRMS).

Preparation of *N*-*tert*-Butylprop-2-en-1-amine. Allyl bromide (1 equiv.) was added dropwise to *t*-butylamine (10 equiv). The clear solution was stirred overnight and became white and cloudy. The reaction was diluted with saturated sodium bicarbonate and extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate and filtered. Careful concentration of the solution (~1/4 original volume) resulted in an ethereal solution of *N*-*tert*-butylprop-2-en-1-amine which was used without further purification.

Preparation of *N*-Benzylprop-2-en-1-amine.[22] A round bottom flask was charged with 5.00 g (47.2 mmol) of benzaldehyde and approximately 150 mL of

dichloromethane was added. To the flask was added 4.04 g (70.8 mmol) of allyl amine followed by 28.4 g (236 mmol) of magnesium sulfate. The resulting reaction mixture was stirred for 16 hours at room temperature under argon. The reaction was then filtered and was concentrated. The clear residue was dissolved in approximately 50 mL of methanol and cooled in an ice bath. Sodium borohydride (3.90 g, 104 mmol) was added in small portions and the reaction was stirred for 3 hours after reaching room temperature. The reaction was quenched with approximately 250 mL of saturated sodium bicarbonate and extracted with approximately 450 mL of diethyl ether. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo yielding 4.57 g (66 %) of a pale yellow oil. The product was used without further purification. Spectral properties were consistent with previously reported data.[22]

Preparation of *N*-(2,3,4,5,6-Pentamethylbenzyl)prop-2-en-1-amine. This molecule was prepared using a similar procedure developed for *N*-benzylprop-2-en-1-amine using 1.40 g of pentamethylbenzaldehyde (7.70 mmol) and yielded 0.800 g (57 %) of the expected product. ^{1}H NMR (400 MHz, benzene-d_6) δ = 5.53 (td, J = 6.5, 16.8, 1H), 5.09 (dd, J = 13.6, 42.8, 2H), 3.74 (s, 2H), 3.23 (d, J = 6.4, 2H), 2.27 (s, 6H), 2.12 (m, 9H), amine (NH) resonance not observed.

Preparation of *N*-Allyl-4-methylbenzenesulfonamide.[23] A round bottom flask was charged with 6.00 g (105 mmol) of allyl amine and approximately 200 mL of dichloromethane. At ambient temperature, 5.70 g (30.0 mmol) of tosyl chloride was added in small portions over the course of five minutes. The resulting reaction mixture was stirred for 16 hours resulting in a cloudy suspension. Approximately 150 mL of water was then added to the flask and the layers separated. The aqueous layer was

extracted with 225 mL of dichloromethane and the organic fractions were combined and dried over pulverized potassium carbonate. Removal of the solvent in vacuo yielded 5.6 g (88 %) of a white solid identified as the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75 (d, 2H), 7.32 (d, 2H), 5.70 (m, 1H), 5.14 (dd, J = 14.0, 43.0, 2H), 4.40 (br s, 1H), 3.59 (m, 2H), 2.43 (s, 3H). Other properties were consistent with previously reported data.[23]

Preparation of 4-Methyl-*N*-(prop-2-ynyl)benzenesulfonamide.[24] A similar procedure to that used for the preparation of *N*-allyl-4-methylbenzenesulfonamide was used employing 1.76 g (32.0 mmol) of propargyl amine. The desired product was isolated as a pale yellow solid (4.70 g, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.3, 2H), 7.32 (d, J = 8.2, 2H), 4.65 (s, 1H), 3.83 (dd, J = 2.4, 5.8, 2H), 2.43 (s, 3H), 2.10 (t, J = 2.5, 1H). Other properties were consistent with previously reported data.[24]

Preparation of 1-Bromobut-2-yne.[25] To approximately 160 mL of anhydrous dichloromethane was added 14.9 g (57.1 mmol) of PPh_3. The flask containing this solution was then cooled in an ice bath. Under an argon atmosphere, 9.14 g (57.1 mmol) of Br_2 was added dropwise, forming a cloudy, pale yellow solution. The mixture was stirred for one hour at 0 ºC. To the yellow reaction mixture 4.00 g (57.1 mmol) of but-2-yn-1-ol was added dropwise. The resulting reaction mixture was stirred for one hour forming a clear yellow solution. Approximately 500 mL of pentane was added to precipitate the Ph_3PO byproduct. The mixture was filtered through a plug of silica gel and then rinsed with an additional 200 mL of pentane. Careful concentration of the filtrate resulted in the isolation of 8.12 g of a clear oil with a strong, acrid odor. As determined by ^{1}H NMR spectroscopy, the oil was ~79 %

w/w 1-bromobut-2-yne in pentane (6.4 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.90 (d, J = 2.4, 2H), 1.88 (s, 3H). Other properties are consistent with previously reported data.[25]

Preparation of But-2-ynyl Methanesulfonate. 2-butyn-1-ol (2.0 mL) was added to 30 mL of anhydrous dichloromethane. Under argon, 4.0 mL of freshly distilled triethylamine was added followed by stirring at 0 ºC for twenty minutes. Mesyl chloride (2.2 mL) was added dropwise resulting in a cloudy, pink solution. Stirring was continued at room temperature for thirty minutes. The reaction was quenched with 30 mL of water followed by successive extractions with 3 x 50 mL of dichloromethane. The organic layer was passed through a short silica plug and evaporated to yield 2.50 g (65 %) of a pale yellow oil). Spectral and physical properties are consistent with previously reported data.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.81 (t, J =2.3, 2H), 3.09 (s, 2H), 1.87 (m, 3H).

Preparation of But-2-ynyl Tosylate.[27] 2-butyn-1-ol (2.0 mL) was added to 50 mL dry diethyl ether. The reaction mixture was cooled to 0 ºC and tosyl chloride (5.36 g, 28.1 mmol) was added in small portions. Powdered potassium hydroxide (15.8 g) was added slowly to prevent frothing over. The reaction was stirred overnight and warmed to room temperature. Approximately 200 mL of water were added and the aqueous phase was extracted with 3 x 75 mL of ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude material was recrystallized from ethyl acetate/hexanes (1:8) to yield 3.6 g (57.4 % yield) of a pale yellow solid. Spectral and physical properties were consistent with previously reported data.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 8.1, 1H), 7.34 (d, J = 8.1, 1H), 4.66 (d J = 2.3, 1H), 2.44 (s, 2H), 1.72 (t, J = 1.9, 2H).

Preparation of Diethyl 2-allylmalonate. Magnesium turnings (1.3 g, 53 mmol) and 8.0 mL ethanol were combined in 100 mL round bottom flask. Carbon tetrachloride (0.5 mL) was added and the suspension was refluxed under argon for one hour. The reaction mixture became thick and white. Diethyl malonate (8.0 g, 50 mmol) in 10 mL of ethanol was added and heating was continued for three additional hours resulting in a dark green solution. The solution was cooled to room temperature and 6.0 mL of ethyl chloroformate in 10 mL THF was added. Heating was continued for one more hour followed by stirring overnight at room temperature. The reaction was quenched with saturated ammonium chloride followed by extraction with 225 mL of ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The resultant clear oil was added to 10 mL hexane and cooled in the freezer overnight which deposited colorless needles, which were collected on a frit (3.40 g, 29 % yield). The needles melted upon warming to room temperature resulting in the isolation of triethyl methanetricarboxylate, which was used without further purification. Spectral and physical properties were consistent with previously reported results.[28] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.38 (s, 1H), 4.26 (q, 6H), 1.27 (t, J = 7.1, 9H).

A solution of sodium ethoxide (1.10 g, 14.7 mmol) in 5 mL of ethanol was prepared and cooled in an ice bath. To the ethanolic solution was added, dropwise, triethyl methanetricarboxylate (3.40 g, 15.0 mmol) in 15 mL diethyl ether. Upon the addition, a white precipitate formed, which was isolated via filtration. The white solid was washed with diethyl ether and dried. Sodium triethyl methanetricarboxylate was isolated as white flowing powder (3.60 g, 96 % yield). Physical properties were consistent with previously reported results.[28]

The sodium salt was added to 40 mL of DMF/toluene (1:1) followed by allyl bromide (1.94 g, 16.0 mL). The mixture was heated to reflux for one hour during

which a white precipitate formed. The reaction was cooled and diluted with 150 mL of toluene, which was washed with 3 x 100 mL of water. The organic layer was washed with 100 mL of brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resultant yellow oil (2.86 g, 75 % yield) was identified as triethyl but-3-ene-1,1,1-tricarboxylate. Spectral and physical properties of product were consistent with previously published reports.[29] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (ddt, J = 7.2, 10.1, 17.2, 1H), 5.11 (ddd, J = 1.4, 8.7, 10.2, 2H), 4.24 (q, J = 7.1, 6H), 2.89 (dd, J = 10.8, 17.0, 2H), 1.27 (t, J = 7.1, 9H).

Sodium ethoxide (0.870 g, 12.8 mmol) was added to 20 mL of THF. The tricarboxylate was dissolved in 20 mL of THF and added to the sodium ethoxide solution. The addition was completed under a stream of argon and the resulting mixture was stirred for one hour. Hydrochloric acid (15 mL, 15 mmol) was added followed by 50 mL of water. The aqueous layer was extracted with diethyl ether. The organic layer was washed with saturated sodium bicarbonate and brine. Concentration of the organic layer yielded 1.83 g of a yellow oil (87 % yield). Isolated product had spectral and physical properties which were consistent with previously published reports.[30] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.77 (ddt, J = 6.8, 10.2, 17.0, 1H), 5.08 (ddd, J = 1.3, 11.3, 13.6, 2H), 4.18 (q, 6H), 3.41 (t, J =7.6, 1H), 2.63 (t, J = 7.2, 2H), 1.26 (t, J = 7.1, 6H).

Preparation of *N*-Allyl-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide.[31] A round bottom flask was charged with 2.00 g (9.56 mmol) of 4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide, 5.30 g (38.2 mmol) anhydrous potassium carbonate and approximately 100 mL of acetonitrile. Allyl bromide (2.30 g, 19.0 mmol) was added dropwise and the resulting solution was heated to reflux overnight. After sixteen hours, the reaction mixture was cooled and the acetonitrile was removed in vacuo.

Approximately 150 mL of saturated sodium bicarbonate was added to the residue and the aqueous solution was extracted with 225 mL of dichloromethane. The organic layers were collected and combined and dried over magnesium sulfate. The mixture was filtered and concentrated to yield a pale yellow solid. The product was dissolved in dry diethyl ether and passed through dried neutral alumina. Evaporation of diethyl ether resulted in isolation of 1.75 g (74%) of a white solid identified as the desired product. ^{1}H NMR (400 MHz, benzene-d_6) δ = 7.73 (d, J = 8.3, 2H), 6.76 (d, J = 8.2, 2H), 5.50 (ddt, J = 6.5, 10.1, 16.6, 1H), 5.06 – 4.83 (m, 2H), 3.93 (d, J = 2.4, 3H), 3.76 (d, J = 6.4, 3H), 1.89 (s, 4H), 1.50 (t, J = 2.4, 1H). Other properties were consistent with previously reported data.[31]

Preparation of *N*-*tert*-Butyl-*N*-(prop-2-ynyl)prop-2-en-1-amine. This compound was prepared using a method similar to that used for *N*-allyl-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide with 0.61 g (5.1 mmol) of propargyl bromide and 0.40 g (3.5 mmol) of *N*-*tert*-butylprop-2-en-1-amine. This procedure yielded 0.30 g (57 %) of the desired product as a light yellow oil. Spectral properties consistent with previous reports.[32] ^{1}H NMR (400 MHz, C_6D_6) δ = 5.79 (dq, J = 6.2, 10.9, 1H), 5.29 (d, J = 17.1, 1H), 5.04 (d, J = 10.1, 1H), 3.45 (d, J = 1.8, 2H), 3.28 (d, J = 6.1, 2H), 1.86 (m, 1H), 1.09 (s, 9H).

Preparation of *N*-Benzyl-*N*-(prop-2-ynyl)prop-2-en-1-amine.[33] This compound was prepared in a manner similar to that used for *N*-allyl-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide using 0.85 g (7.1 mmol) of propargyl bromide and 0.90 g (4.9 mmol) of *N*-benzylprop-2-en-1-amine (0.90 g, 4.9 mmol). The desired product (0.81 g, 69% yield) was isolated as a yellow oil. Product properties similar to previously reported data. ^{1}H NMR (400 MHz, C_6D_6) δ = 7.37 (d, J = 7.5, 2H), 7.17 (t,

J = 8.1, 2H), 7.09 (t, J = 7.1, 1H), 5.79 (ddt, J = 6.4, 10.2, 16.6, 1H), 5.11 (dd, J = 13.7, 75.2, 2H), 3.59 (s, 2H), 3.22 (t, J = 4.0, 2H), 3.12 (d, J = 6.4, 2H), 1.90 (t, J = 1.9, 1H). Spectral properties were consistent with previously reported data.[33]

Preparation of *N*-(Pentamethylbenzyl)-*N*-(prop-2-ynyl)prop-2-en-1-amine. This compound was prepared in a similar manner to *N*-allyl-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide using 0.714 g (4.8 mmol) of propargyl bromide and 0.800 g (3.69 mmol) of (pentamethylbenzyl)-prop-2-en-1-amine. The desired product (0.750 g, 79 %) was isolated as a white powder. ^{1}H NMR (400 MHz, benzene-d_6) δ = 5.78 (m, 1H), 5.24 (d, J = 17.1, 1H), 5.00 (d, J = 10.1, 1H), 3.78 (s, 2H), 3.38 – 3.15 (m, 4H), 2.38 (s, 1H), 2.10 (s, 1H), 1.95 (s, 1H).

Preparation of *N*-Allyl-*N*-(but-2-ynyl)-4-methylbenzenesulfonamide.[25] This compound was prepared in a similar manner to *N*-allyl-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide using 0.55 g (4.14 mmol) of 1-bromobut-2-yne (0.55 g, 4.14 mmol) and 0.73 g (3.5 mmol) of *N*-allyl-4-methylbenzenesulfonamide. The desired product (0.63 g, 69% yield) was isolated as a white solid. The spectral and physical properties of the product were consistent with previously published reports.[25]

Preparation of Diethyl 2-allyl-2-(prop-2-ynyl)malonate. Diethyl 2-allylmalonate (1.0 g, 5.0 mmol) was added to 10 mL of diethyl ether and cooled in an ice bath. Sodium ethoxide (360 mg, 5.0 mmol) was added to 5 mL of ethanol. The ethanolic solution was added dropwise to the ethereal solution and the reaction was stirred vigorously for ten minutes. Propargyl bromide (713 mg, 6.0 mmol) was added dropwise to the reaction mixture which was stirred for one hour allowing ambient temperature to be reached. Brine was added and the aqueous layer was extracted with

3 x 100 mL of diethyl ether. The organic layers were combined, dried over magnesium sulfate and filtered. The solution was concentrated to yield 1.1g (92 %) of a pale yellow oil. Properties consistent were with previously reported data.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (ddt, J = 7.4, 10.0, 17.4, 1H), 5.23 – 5.08 (m, 2H), 4.20 (q, J = 7.3, 4H), 2.82 –2.78 (m, J = 4.8, 4H), 2.04 – 1.98 (m, 1H), 1.25 (t, J = 7.3, 6H).

General Preparation of Alkynyl Allyl Ethers. The alkynol (11.0 mmol) was added dropwise to a cooled solution sodium hydride (25 mmol) in diethyl ether/DMF (20 mL, 10:1). The reaction mixture was stirred under argon for one hour and allowed to warm to room temperature. The reaction was cooled in an ice bath. Allyl bromide (9.5 mmol) in 5 mL of diethyl ether was added dropwise. The reaction was stirred overnight and quenched with brine. The layers were separated and the organic layer was washed with water to remove DMF. The organic layer was dried over magnesium sulfate and filtered. Careful rotary evaporation resulted in isolated of the alkynyl allyl ether, which were dried by passing through alumina in the dry box. Spectral properties are consistent with previously reported data.[35]

Preparation of *N*-Allyl-*N*-benzylbut-2-yn-1-amine.[36] This compound was prepared in a similar manner to *N*-allyl-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide using 0.55 g (4.14 mmol) of 1-bromobut-2-yne and 0.696 g (3.5 mmol) of *N*-allylbenzylamine. The desired product was isolated as 0.53 g (61 %) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 – 7.23 (m, 5H), 5.88 (ddt, J = 17.1, 10.3, 6.4, 1H). 5.26 (dq, J = 17.3, 1.7, 1H), 5.16 (dd, J = 10.3, 1.5, 1H), 3.62 (s, 2H), 3.24 (q, J = 2.3, 2H), 2.43 (s, 3H), 2.10 (t, J = 2.5, 1H).

Preparation of *N*-Allyl-4-methyl-*N*-(3-(trimethylsilyl)prop-2-ynyl)benzenesulfonamide.[37] A round bottom flask was charged with 0.150 g (0.60 mmol) of *N*-allyl-4-methylbenzenesulfonamide and approximately 20 mL diethyl ether and cooled to -35 ºC in dry box freezer. *n*-Butyl lithium in hexane (2.67 mL, 1.6 M, 0.60 mmol) was added dropwise to the stirring enyne and stirred for one hour allowing the reaction to reach room temperature. After one hour, the reaction was cooled to -35 ºC in dry box freezer. Trimethylsilylchloride (0.065 g, 0.60 mmol) was added to the mixture dropwise. The solution became cloudy and white and was stirred for 16 hours at room temperature. The reaction was filtered through celite and concentrated. Recrystallization of the yellow residue resulted in the isolation 0.110 g (57 %) of a white solid. ^{1}H NMR (400 MHz, benzene-d_6) δ = 7.74 (d, J = 8.3, 2H), 6.80 (d, J = 8.0, 2H), 5.54 (ddt, J = 6.5, 10.1, 16.6, 1H), 5.08 (dd, J = 1.5, 16.9, 1H), 4.91 (dd, J = 1.3, 10.1, 1H) 4.02 (s, 2H), 3.8 (d, J = 6.4, 1H), 1.94 (s, 3H), -0.6 (s, 9H). Spectral properties were consistent with previously reported data.[37]

Preparation of (*Z*)-*N*-(But-2-enyl)-*N*-(but-2-ynyl)-4-methylbenzenesulfonamide. Prepared according to previously reported procedure.[38]

Preparation of *N*,*N*-Di(but-2-ynyl)-4-methylbenzenesulfonamide.[39] A 100 mL round bottom flask was charged with 1.61 g (11.7 mmol) of potassium carbonate, approximately 15 mL of dimethylformamide and 0.500 g (2.92 mmol) of 4-methylbenzenesulfonamide. The resulting suspension was stirred for one hour at room temperature. After this time, 0.894 g (6.72 mmol) of 1-bromobut-2-yne was added dropwise and the reaction mixture was stirred at room temperature for 16 hours. Approximately 100 mL of water was then added and the desired product extracted with 200 mL of diethyl ether. The combined organic layers were successively washed

with 3 x 30 mL of water (3x, 30 mL), then 30 mL of brine and dried over magnesium sulfate. Evaporation of the diethyl ether resulted in the isolation of a yellow solid. The yellow solid was dissolved in diethyl ether, passed through dry neutral alumina, and concentrated to yield 0.610 g (76 %) of a white powder. Spectral properties are consistent with previously reported data.[39]

Preparation of *N*,*N*-Di(but-2-ynyl)aniline. To a suspension of 2.97 g (138 mmol) of potassium carbonate in 20 mL of a 1:4 water:ethanol mixture was added 0.700 g (5.38 mmol) of anilinium chloride. A few milligrams of 18-crown-6 were then added to the suspension, which was then stirred for 30 minutes at room temperature. To the reaction flask, 1.64 g (12.4 mmol) of 1-bromobut-2-yne was added dropwise. The resulting reaction mixture was then heated to reflux for sixteen hours. Upon cooling, 75 mL of brine was added followed by 225 mL of diethyl ether. Following extraction with diethyl ether, the organic layers were combined and dried over magnesium sulfate and filtered. Evaporation of the diethyl ether yielded a pale yellow solid which as purified by passage through a short neutral alumina column. Evaporation of the solvent yielded 0.575 g (54.5 %) of a white solid identified as the title compound, which had spectral and physical properties to previously published data.[40] ^{1}H NMR (300 MHz, benzene-d_6) δ = 7.19 (t, J = 8.0, 2H), 6.96 (d, J = 8.1, 2H), 6.81 (t, J = 7.3, 1H), 4.02 (d, J = 2.1, 4H), 1.41 (s, 6H).

Preparation of Diethyl 2,2-di(but-2-ynyl)malonate. Under argon, sodium hydride (0.615 g 25.6 mmol) was added to a mixture of 25 mL toluene/50 mL of DMF. The mixture was cooled in an ice bath. Diethyl malonate (1.28 g, 8.0 mmol) was dissolved in 8 mL of DMF and added dropwise. The solution was stirred for one hour. 2-butyn-4-tosylate (3.6 g, 16.7 mmol) dissolved in 8 mL DMF and added dropwise to the

reaction mixture. The reaction was stirred overnight and warmed to room temperature. A mixture of water/toluene (50 mL/100 mL) was used to quench the reaction. The layers were separated and the organic layer was collected. The remaining aqueous layer was washed with 100 mL of toluene and combined with the other organic layer. The combined organic layers were washed with 75 mL of water, 50 mL of brine and dried over magnesium sulfate. The drying agent was removed by filtration and the volatiles were removed to yield 2.0 g (95%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 4.19 (q, 4H), 2.87 (q, 4H), 1.72 (t, J =2.5, 6H), 1.23 (t, J = 7.1, 6H). Spectral properties consistent with previously reported data [41]

Preparation of *N*-Benzyl-*N*-(but-2-ynyl)but-2-yn-1-amine. Benzyl amine (0.701 g, 6.54 mmol) was added to 20 mL of acetonitrile in a 50 mL round bottom flask. Potassium carbonate (3.61 g, 26.2 mmol) was added to the flask and stirred for 30 minutes. 4-bromobut-2-yne (2.0 g, 15.0 mmol) was added dropwise to the solution and the resulting mixture heated to reflux overnight. After this time, the acetonitrile was removed under reduced pressure and the residue was dissolved in 50 mL saturated sodium bicarbonate. The aqueous mixture was extracted with 100 mL of diethyl ether and separated. The organic layer was collected, dried over sodium sulfate, filtered, and dried. The resulting yellow oil was concentrated to yield 1.10 g (79.7 %) of the desired product. Spectral properties of product are similar to previously reported data.[42] ^{1}H NMR (benzene-d_6) δ = 7.35-7.10 (m, 5H), 3.54 (s, 2H), 1.72 (t, J =2.5, 6H), 1.23 (t, J = 7.1, 6H).

General Catalytic Reaction Procedure. In a dry box, a thick-walled glass vessel was charged with 10 mg (0.017 mmol) of 1-$(N_2)_2$, approximately 0.800 mL of toluene or benzene. The vessel was then transferred into a liquid nitrogen cooled cold well until

the contents were frozen. All substrates that were used in the iron-catalyzed reductive cyclization were furthered purified (and dried) by passage through a short pipette column of activated neutral alumina using pentane or ether as an eluent. The enyne or diyne substrate (0.340 mmol) was dissolved in 0.20 mL of solvent (toluene or benzene) and added dropwise to the frozen catalyst solution. The vessel was transferred to the high vacuum line, submerged in liquid nitrogen and evacuated. While at this temperature, one atmosphere of dihydrogen was added. Upon thawing, the solution became increasingly red-brown. Once at 23 ºC, the reactions were stirred for the specified amount of time. Once the reaction was complete, the reaction was quenched with ~3 mL methanol. Upon quenching, the reaction mixture was filtered to remove iron oxide. The filtrate was concentrated and methanol (~3 mL) was added to precipitate the remaining free ligand, which was removed by filtration. The resultant methanolic solution was concentrated, dissolved in ethyl acetate/hexanes and passed through a silica plug to yield pure cyclized product.

Characterization of Cyclization Products.

Assignment of Stereochemistry of Dimethylcyclopentane Derivatives. A stoichiometric amount of zirconocene was added to the corresponding 1,6-heptadiene. The stereochemistry of the resulting metallocycle was assigned by ^{1}H-NMR spectroscopy and then hydrolyzed to release the dimethylcyclopentane derivative. The stereochemistry (*cis* or *trans*) of the organic fragment was then determined (from the metallocycle) and used to identify the product of hydrogenation of all the terminal enynes in the presence of 1-$(N_2)_2$ under 4 atm of hydrogen. The following dienes were used: *N,N*-diallyl *t*-butylamine, *N,N*-diallyl tosylamine, *N,N*-diallyl benzyl amine, and *N,N*-diallyl-2,3,4,5,6-pentamethylbenzylamine. No attempt was made to separate the diastereomers in the case of 3,4-dimethyl-*N*-tosylpyrrolidine.

3,4-Dimethyl-1-tosylpyrrolidine. Mixture of isomers: *cis/trans:* 3/1 as determined by GCMS. *cis*-isomer: ^{1}H NMR (400 MHz, benzene-d_6) δ = 7.82 (d, J = 7.9, 2H), 6.84 (d, J = 7.9, 2H), 3.28 (dd, J = 6.3, 9.6, 2H), 2.86 (dd, J = 5.4, 9.6, 2H), 1.91 (s, 3H), 1.53 (m, 1H), 0.35 (d, J = 6.4, 14H). *trans*-isomer distinctive peaks: δ = 3.43 (d, J = 7.1, 2H), 2.69 (t, J = 9.2, 1H), 0.45 (d, J = 5.8, 4H). Isolated as a white solid (79%). HRMS: 253.1136 (calc'd); 253.1146 (found).

***cis*-3,4-Dimethyl-1-benzylpyrrolidine.** ^{1}H NMR (300 MHz, benzene-d_6) δ = 7.45 – 7.10 (m, 5H), 3.51 (s, 2H), 2.86 (dd, J = 5.8, 10.0, 3H), 2.14 (m, 2H), 1.95 (dd, J = 6.9, 8.9, 2H), 0.78 (d, J = 6.6, 6H). Only *cis*-isomer present as determined by GCMS. LR GCMS (m/Z): 189.1, 132.0, 112.1, 98.1, 91.0, 65.0 (*cis* isomer). Isolated as a pale yellow oil which was analytically pure by NMR (71%). Data consistent with previously reported results.[43] Completely saturated amine only detected by GCMS (3.7% relative to *N*-benzyl-3,4-dimethylpyrrolidine). LR GCMS (m/Z): 191.1, 172.1, 91.0, 65.0 (dipropylbenzylamine).

***cis*-1-*tert*-Butyl-3,4-dimethylpyrrolidine.** ^{1}H NMR (400 MHz, benzene-d_6) δ = 2.82 – 2.76 (m, 2H), 2.14 (dd, J = 6.0, 8.6, 2H), 2.05 – 1.95 (m, 2H), 0.95 (s, 9H), 0.75 (d, J = 6.3, 6H). Only *cis*-isomer as determined by GCMS. Yield of *cis*-3,4-dimethyl-*N*-*tert*-butylpyrrolidine determined to be 68% by comparison to internal standard (10 mL CH_2Cl_2) using ^{1}H-NMR spectroscopy. HRMS: 253.1136 (calcd); 253.1146 (found). By GCMS, (3-*tert*-butyl-3-azabicyclo[3.2.0]heptane shown to be minor product, which resulted from hydrogenation of alkyne to alkene followed by isomerization (of diallyl-*t*-butylamine) to 5,4 bicycle by (^{iPr}PDI)Fe fragment.[14]

3,4-Dimethyl-1-(2,3,4,5,6-pentamethylbenzyl)pyrrolidine. Under 4 atm of hydrogen, by GCMS, only partial conversion to pyrrolidine (57.5 %). HRMS: 259.2300 (calc'd), 259.1456 (found). LR GCMS (m/Z): 260.1, 259.1 (*M)*, 162.1, 161.1, 160.2, 145.1. The remainder of the area was unreacted enyne (26.9%) and fully saturated amine (15.6%). LR GCMS (m/Z): 262.2, 261.1 (*M*), 232.1, 161.1, 160.1. When reaction was run under 1 atm H_2, and the reaction time was extended to 24 hours, the product could be isolated cleanly. The pyrrolidine was isolated cleanly as a white powder 54% yield).

3-Methyl-4-methylenetetrahydrofuran. ^{1}H NMR (300 MHz, benzene-d_6) δ = 4.75 – 4.64 (m, 1H), 4.26 (d, J = 12.8, 1H), 4.15 (d, J = 13.4, 1H), 3.83 (m, 1H), 3.20 (m, 1H), 2.38 (m, 1H), 0.68 (d, 3H). 95% yield as compared to 10 mL chloroform as internal standard. Product of reductive cyclization in agreement with previously reported data.[44] Extended reaction times (24 hours) result in the partial hydrogenation of the exocyclic double bond (53% conversion) to yield a mixture of 61% *cis*-3,4-dimethyl tetrahydrofuran to 39% *trans*-3,4-tetrahydrofuran. *cis* isomer: ^{1}H NMR (400 MHz, benzene-d_6) δ = 3.84 (t, 2H), 3.35 (dd, 2H), 1.93 (m, 2H), 0.71 (d, 6H).[45] *trans*-isomer distinctive peak: 3.26 (m, 2H). Other peaks for *trans*-isomer overlap with exo-methylene product.

(*Z*)-4-Methyl-*N*-(2-(4-methyl-1-tosylpyrrolidin-3-ylidene)ethyl)-*N*-propylbenzene sulfonamide. ^{1}H NMR (400 MHz, benzene-d_6): δ = 7.77 (d, J = 8.2, 2H), 7.60 (d, J = 8.2, 2H), 6.83 (d, J = 8.1, 2H), 6.77 (d, J = 8.1, 2H), 4.86 (s, 1H), 3.83 (dd, J = 14.7, 66.4, 2H), 3.38 (m, 3H), 2.95 – 2.75 (m, 2H), 2.45 (t, J = 8.8, 1H), 2.17 (s, 1H), 1.91 (s, 3H), 1.86 (s, 3H), 1.30 – 1.10 (m, 2H), 0.65 (t, J = 7.4, 3H), 0.52 (d, J = 6.7, 3H). Isolated as a white solid (83.1%). Structure assigned by ^{1}H-COSY NMR experiments.

Diethyl-3,4-dimethylcyclopentane-1,1-dicarboxylate. Yield of the dimethylcyclopentane determined to be 74.1% by GCMS with remaining 25.9% determined to be diethyl 2,2-dipropylmalonate. Reaction products not separated. Yield (of 74%) was determined by conversion of reactant to product using GCMS. Mixture of isomers observed for dimethylcyclopentane-1,1-dicarboxylate - 3.4:1 *cis*:*trans*. LR GCMS (m/Z) : 197.4 (loss of EtO), 173.4, 153.3, 141.4, 127.2, 95.2 (*cis* and *trans* isomers have similar fragmentation pattern). Analytical data consistent with previously published reports for diethyl ester.[46] Data also consistent with previously reported dimethyl ester.[47]

(*Z*)-1-Benzyl-3-ethylidene-4-methylpyrrolidine. ^{1}H NMR (400 MHz, benzene-d_6) δ = 7.19 (m, 5H), 5.08 (s, 1H), 3.62 (s, 2H), 3.36 – 3.24 (m, 2H), 2.81 – 2.72 (m, 1H), 2.58 (m, 1H), 1.94 (t, J = 8.1, 1H), 1.36 (d, J = 6.5, 3H), 0.98 (d, J = 6.8, 3H). Isolated as a yellow oil (71%). HRMS: 201.1517 (calcd); 201.1567 (found).

(*Z*)-3-Ethylidene-4-methyl-1-tosylpyrrolidine. ^{1}H NMR (400 MHz, benzene-d_6) δ = 7.76 (d, J = 8.1, 3H), 6.78 (d, J = 7.9, 3H), 4.83 (m, 1H), 3.82 (d, J = 65.6, 2H), 3.45 (t, J =8.41, 1H), 2.54 (t, J = 8.92, 1H).1.87 (s, 3H), 0.65 (d, J = 6.7, 3H). Compound was previously characterized and matches literature data.[12] Isolated as a white solid (79%).

(*Z*)-3-Ethylidene-4-methyltetrahydrofuran. ^{1}H NMR (400 MHz, benzene-d_6) δ = 5.08 (m, 1H), 4.33 (d, J = 12.8, 1H), 4.23 (d, J = 13.4, 1H), 3.91 (m, 1H), 3.37 (m, 1H), 2.38 (m, 1H), 1.45 (d, 3H), 0.85 (d, 3H). Product not isolated because of volatility, but yield determined to be 62% by comparison to internal standard of 10 mL of chloroform. HRMS: 112.0888 (calcd); 112.1007 (found). Compound

characterization similar to previously reported data.[48]

(*Z*)-3-Methyl-1-tosyl-4-((trimethylsilyl)methylene)pyrrolidine.

^{1}H NMR (300 MHz, benzene-d_6) δ = 7.78 (d, J = 8.1, 2H), 6.80 (d, J = 7.9, 2H), 5.19 (s, 1H), 4.14 (d, J = 14.6, 1H), 3.90 (d, J = 14.7, 1H), 3.55 – 3.40 (m, 1H), 2.53 (t, J = 8.9, 1H), 1.91 (m, 1H), 1.86 (s, 3H), 0.68 (d, J = 6.7, 2H), -0.01 (s, 9H). Compound was previously characterized and matches literature data.[12]

(*Z*)-3-Ethyl-4-ethylidene-1-tosylpyrrolidine. ^{1}H NMR (400 MHz, benzene-d_6) δ = 7.78 (d, J = 8.1, 3H), 6.80 (d, J = 7.9, 3H), 4.86 (m, 1H), 3.84 (d, J = 65.6, 2H), 3.46 (t, J =8.41, 1H), 2.54 (t, J = 8.92, 1H), 1.87 (s, 3H), 0.65 (pent, 2H), 0.52 (t, 3H). HRMS: 279.1293 (calcd); 279.1351 (found). When *cis*-crotyl-2-butynyl-tosylamine was exposed to 4 atm of hydrogen in the presence of 1-$(N_2)_2$ for three hours the main product was dibutyltosylamine (73%, m/Z = 283) with the minor product being the expected pyrrolidine (15%. m/Z = 279), and the remainder of the mass was partially hydrogenated isomers. When 1 atm of hydrogen (exposure time of 8 hr) is used, the ratio of completely saturated amine to expected pyrrolidine is 6:4. When less than 1 atmosphere of hydrogen is used, the reaction is very sluggish even after 24 hours. Clean and complete conversion to pyrrolidine could only be accomplished with stoichiometric iron or using phenyl silane as hydrogen source.

(3*Z*,4*Z*)-3,4-Diethylidene-1-tosylpyrrolidine. Compound was previously characterized and matches literature data.[12] ^{1}H NMR (benzene-d_6) δ = 7.78 (d, 2H), 6.79 (d, 2H), 5.43-5.38 (m, 2H), 3.98 (s, 4H), 1.88 (s, 3H), 1.23 (d, 6H).

(3*Z*,4*Z*)-3,4-Diethylidene-*N*-benzylpyrrolidine. ^{1}H NMR (300 MHz, benzene-d_6) δ = 7.40 (d, 7.38 Hz) 2H), 7.22–7.10 (m, 2H), 5.67 (m, 2H), 3.57 (s, 2H), 3.24 (s, 4H), 1.45 (d, J = 6.7 Hz, 6H). Isolated as an off-white solid (97%). HRMS: 213.1517 (calcd); 213.1111 (found).

(3*Z*,4*Z*)-3,4-Diethylidene-1-phenylpyrrolidine. ^{1}H NMR (300 MHz, benzene-d_6) δ = 7.30 (m, 2H), 6.86 (t, J = 7.3, 1H), 6.53 (d, J = 7.9, 2H), 5.73 – 5.62 (m, 2H), 3.83 (m, 4H), 3.11 – 3.01 (m, 2H), 1.48 (d, J = 7.1, 6H). Isolated as a yellow solid (67%) with remaining mass being dibutylphenylamine, which was separated from desired product by washing with cold pentane. Independent preparation was achieved from butyl bromide and aniline.

(3*E*,4*E*)-Diethyl 3,4-diethylidenecyclopentane-1,1-dicarboxylate. ^{1}H NMR (400 MHz, C_6D_6) δ 5.73 (s, 2H), 3.95 (q, J = 7.1, 6H), 3.21 (s, 4H), 1.57 (d, J = 6.8, 6H), 0.90 (t, J = 7.1, 6H). LR GCMS (m/Z): 266.6, 221.5, 192.4, 177.4, 163.3. Yield reported as conversion which was determined by GCMS to be 57.6%. In this case, yield was 58% as determined by GCMS, but product mixture was not separated. Physical and spectroscopic properties are similar to previously reported methyl ester.[12] GCMS showed presence of diethyl 2,2-dibutylmalonate (complete alkyne reduction), which was confirmed by independent synthesis from diethyl malonate and butyl bromide. LR GCMS (m/Z): 227.6, 216.5, 199.5, 183.5, 173.4.

Stoichiometric Reactions

Stoichiometric Reactions of 1-$(N_2)_2$ and Enynes. 1-$(N_2)_2$ (20 mg, 0.034 mmol) was added to 0.800 mL benzene-d_6 in a J. Young tube in the dry box. The substrate (0.034 mmol) was then added and a red solution immediately formed. The ^{1}H NMR spectrum

was taken revealing a paramagnetic compound. Over the course of three hours, the paramagnetic resonances were reduced in intensity and the solution turned from red to brown. The resulting ^{1}H NMR spectrum revealed only the cyclized product and presumably a ^{1}H NMR silent compound. Upon quenching with water, dehydrogenated ligand and the cyclized dieyne were observed in the ^{1}H NMR spectrum. Conversions were greater than 95% (by ^{1}H NMR) for E = TsN, BnN, and O. Also, the TMS-protected alkyne with E= TsN underwent the same reaction. The reaction was also successful with *cis*-crotyl-2-butynyltosylamine.

Characterization of Addition Product of Allyl-2-butynyltosylamine and 1-$(N_2)_2$. The ^{1}H NMR spectrum was obtained, but even within a few minutes, degradation of the intermdiate to the pyrrolidine and NMR silent olefin compound is observed. As a result, a crystal of this compound could not be grown. Magenetic measurement (Evans, NMR) resulted in a magnetic moment of 4.7 μ_B, which is consistent with an S = 2 and the intermediate structure that is proposed. ^{1}H NMR (400 MHz, C_6D_6) δ 121.4 (*m*-pyr, 204 Hz, 2H), 40.1 (104 Hz), 31.1 (68 Hz), 29.4 (68 Hz), 21.2 (37 Hz), 11.1 (75 Hz), 10.4 (55 Hz), 9.25 (76 Hz), 7.31 (18.4 Hz), 5.1 (81 Hz), 4.8 (68 Hz), 0.22 (134 Hz), -1.5 (191 Hz), -24.1 (Fe-CH_2, 389 Hz, 1H), -27.0 (Fe-CH_2, 407 Hz, 1H), -97.1 (ArN=C(*CH_3*), 1329 Hz, 6H).

Stoichiometric Reactions of 1-$(N_2)_2$ and Diynes. 1-$(N_2)_2$ (20 mg, 0.034 mmol) was added to 0.800 mL toluene in a scintillation vial in the glove box. Substrate (0.034 mmol) was then added as the solution was stirred. Initially, the solution turned from green to red-purple. Over the course of three hours, the red-purple color dissipated to result in a red-brown solution. Upon quenching with water, dehydrogenated ligand and

the cyclized diyne were observed in the ^{1}H NMR spectrum. Conversions were greater than 95% (by ^{1}H NMR) for E = TsN, BnN, PhN, and $(EtO_2C)_2C$.

Kinetic Isotope Effect Measurement. A J. Young NMR tube was charged with 20 mg of 1-$(N_2)_2$ and a solution of 9 mg of 2-butynyl allyl tosyl amine in 0.550 g of benzene-d_6. A J. Young NMR tube was also prepared containing 20 mg of 1-$(N_2)_2$* and a solution of 9 mg of 2-butynyl allyl tosyl amine in 0.550 g of benzene-d_6. The reactions were monitored by ^{1}H NMR spectroscopy. Initially, the solution of the unlabeled dinitrogen compound (and substrate) became dark red and the ^{1}H NMR exhibited paramagnetic resonances. Over the course of 102 minutes, the solution became dark brown and the paramagnetic resonances dissipated in intensity and the resonance for the pyrrolidine appeared in the ^{1}H NMR. For the labeled nitrogen compound, similar observations were made, but the paramagnetic resonances took 588 minutes to dissipate in intensity. The ratio of the reaction times was determined to be 5.8.

The deuterated product was identified as a mixture of d_1-pyrrolidine isotopomers by GCMS based on the observation of a peak at 266 amu. One isomer has deuterium incorporated into the olefinic position and the other isomer has deuterium incorporation into the methyl group. (The mass spectrum of this mixture was different from the natural abundance pyrrolidine as well as the d_2-pyrrolidine). From the ^{1}H NMR spectrum the relative ratio of the d_1-isomers is ~3.5:1 with the major isomer having deuterium incorporation into the exo-methyl group.

To gain a better understanding of the isotope effect, the NMR tube reactions were repeated and monitored by GCMS. Hydrolysis of the metallocycle (labeled or unlabeled) leads to the formation of the pyrrolidine, so iodine was used to quench the metallocylce. Addition of iodine to the metallocycle resulted in the oxidation of the

PDIFe fragment and release of the enyne. The ratio of unreacted enyne to pyrrolidine (calculated as percent conversion) was then measured at various time points and the data is presented in Table 1.2 below.

Table 1.2. Kinetic isotope effect: ratio of unreacted enyne to pyrrolidine.

Time	30 min	60 min	90 min	120 min
% Conv (Proteo)	57 %	84 %	93 %	>99 %
% Conv (Deutero)	11 %	26 %	35 %	49 %

Assuming the initial concentration of the metallocycle was ~ 0.058 M (from mass of nitrogen compound added and enyne), the approximate concentration of metallocycle remaining could be determined as a function of time. This would allow a relative k_H/k_D to be reported for each time point. The data are presented below in Table 1.3.

Table 1.3. Kinetic isotope effect: k_H/k_D.

Time	30 min	60 min	90 min	120 min
Conc. of Metallocycle (Proteo)	0.25 M	0.093 M	0.041 M	~ 0.006 M
Conc. of Metallocycle (Deutero)	0.52 M	0.43 M	0.38 M	0.29 M
k_H/k_D	2.1	4.6	9.3	~51.

Plotting the natural log of the concentration of the metallocycle as a function of time resulted in a linear for both the deutero and proteo species. The calculated first order rate constant from the deuterated intermediate was 1.1×10^{-4} $M^{-1}s^{-1}$ and for the hydrogenated intermediate was 6.6×10^{-4} $M^{-1}s^{-1.}$ The ratio of these rate constants is consistent with a first order process and is consistent with the experiment monitored by ^1H NMR.

Catalytic Deuteration of Selected Substrates. Deuteration experiments were conducted in the same manner as hydrogenations (see above).

Catalytic Deuteration of *N*-Allyl-*N*-(but-2-ynyl)-4-methylbenzenesulfonamide. Deuteration of the substrate under 4 atm of deuterium showed incorporation in the expected places with no deuterium migration detected by ^{2}H NMR spectroscopy.

Catalytic Deuteration of Bis(but-2-ynyl)-4-methylbenzenesulfonamide. Deuteration of the substrate under 4 atm of deuterium showed incorporation in the *exo*-methine positions with no deuterium migration detected by ^{2}H NMR spectroscopy.

Catalytic Seuteration of *N*-Allyl-*N*-propargyl-4-methylbenzenesulfonamide. Deuteration of the substrate under 4 atm of deuterium showed incorporation in the *exo*-methylene position and the methyl group. Subsequent deuteration of the exomethylene group results in the d_4-pyrrolidine. The ratio of 3:1 *cis*:*trans* isomers observed in the hydrogenation of *N*-allyl-*N*-propargyl-4-methylbenzenesulfonamide is also found in the catalytic deuteration.

Reactions Involving Phenylsilane and Enynes.

Catalytic Hydrogenation of Enynes Using Phenylsilane as Hydrogen Source. The general scheme for the reaction is shown below (Figure 1.20).

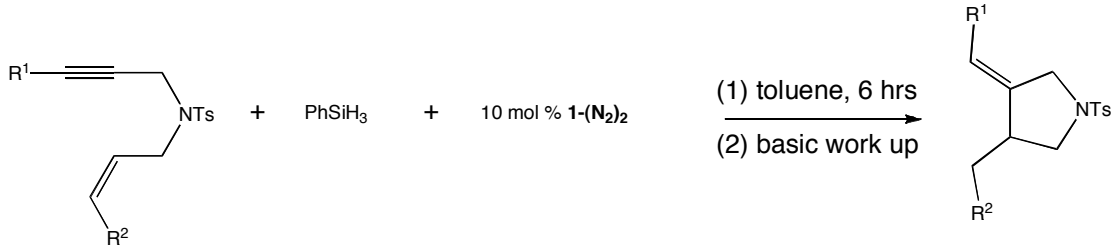


Figure 1.20. General scheme for catalytic hydrogenation of enynes.

Two equivalents of phenyl silane were added to a mixture of 5 mg 1-$(N_2)_2$ (0.0009 mmol, 0.05 equivalents) in 5 mL toluene. Twenty equivalents (0.017 mmol) of the enyne substrate were added and allowed to stir for three to six hours as room temperature. The resulting product was determined to be the pyrrolidine resulting from cyclization of the enyne with phenylsilane as the hydrogen source to liberate the product from the metal. After six hours, the reaction was quenched with 1 M KOH and stirred for ten minutes. The phases were separated and the organic layer was concentrated and then dissolved in methanol. Filtration of the methanolic solution separated the free ligand from the product. The methanolic solution was evaportated and the resulting oil was dissolved in 5 mL ethyl acetate and through a silica plug. Isolated yields are presented in Table 1.4 below.

Table 1.4. Results of catalytic hydrogenation of enynes.

Enyne Substrate	Isolated Yield	Conversion
$R^1 = R^2 = H$	66 %	> 95 %
$R^1 = CH_3$; $R^2 = H$	77 %	> 95 %
$R^1 = R^2 = CH_3$	53 %	> 95 %

***N*-Allyl-*N*-(but-2-ynyl)-4-methylbenzenesulfonamide and 1-$(PhSiH_3)_2$.** 20 mg of 1-$(N_2)_2$ was added to 5 mL of pentane in a 20-mL scintillation vial. Two equivalents of phenylsilane were added resulting in a brownish solution. One equivalent (9 mg) of allyl-2-butynyl-tosylamine was added. The reaction was stirred for twelve hours.

Analysis of the products showed the dehydrogenated coupled phenyl silane (PhH_2Si-SiH_2Ph) and the pyrrolidine product of the catalytic hydrogenation.

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CHAPTER 2

EXPLORATION OF THE IRON-CATALYZED [2π+2π] REACTION: SCOPE, MECHANISM, AND REACTIVITY

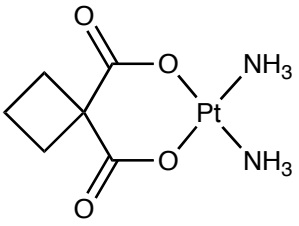
2.1 Abstract

Previously it was reported that treatment of 1,6-dienes with 10 mol % (^{iPr}PDI)Fe(N_2)$_2$ ((^{R}PDI = 2,6-(2',6'-R_2-C_6H_3N=CMe)$_2C_5H_3N$; R= iPr, Me) catalyzed the formation of the [3.2.0]bicyloheptane framework (product A**)** by a [2π+2π] cyclization. Extensions of this work have been investigated and will be described in this chapter. The substrate scope has been expanded to include a series of protected diallylamines as well as other dienes with substitution at the four-position. Taking advantage of the selectivity of this reaction (bridgehead hydrogens are *cis*) enabled the exploration of diastereoselectivity in the [2π+2π] reaction. With the recent discovery of a series of new iron nitrogen compounds in our lab, the effect of catalyst variation was also explored. With less hindered and less reducing catalysts such as [(^{Me}PDI)Fe(N_2)]-μ-(N_2), it was found that certain substrates underwent a second reaction pathway, the formation of 3-methylene-4-methylcyclopentanes (pyrrolidines) (product B**)**. For substrates showing divergent reactivity, increasing the reaction temperature caused an increase in formation of the [2π+2π] product. The mechanism was probed using the reaction between diallyl tosylamine and [(^{Me}PDI)Fe(N_2)]-μ-(N_2). It was found that the reaction between diallyl tosylamine (twenty equivalents) and [(^{Me}PDI)Fe(N_2)]-μ-(N_2) was first order in iron and that the secondary pathway is more complicated than originally thought, given involvement of the aniline methyl group. Currently several more experiments are being conducted to further clarify the mechanism of formation of product B. Lastly, to make this chemistry more amenable to bench top use, a series of (^{R}PDI)Fe(dihalides) were used as catalyst precursors and

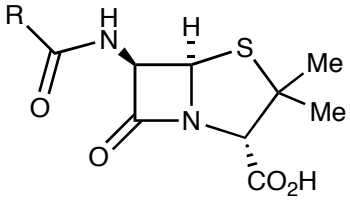
reduced in situ with sodium triethylborohydride to generate competent catalysts for the [2π+2π] reaction of diallylaniline. It was also found that ($^{2,5\text{-di-}t\text{Bu}}$PDI)$FeCl_2$, when reduced with sodium triethylborohydride, will catalyze exclusive formation of product B. The scope of this reaction was fairly broad and resulted in complete conversions.

2.2 Introduction

Molecules that contain cyclobutane rings are important in the chemical synthesis of natural products and various therapeutic agents. Two examples of therapeutic agents that feature a cyclobutane ring are depicted in Figure 2.1. Carboplatin, a very effective anticancer drug, contains a cyclobutane ring, which increases the half-life of the drug and improves selectivity as compared to cisplatin and oxaliplatin.[1] Another important class of pharmaceutical agents containing the cyclobutane structural motif, β-lactam antibiotics, has saved countless lives. The most noteworthy, penicillin, is the first example of this drug class and has been derivatized frequently. Preparing penicillin analogs typically involves semi-synthesis, wherein the antibiotic core is biologically prepared by microorganisms, and the rest of the molecule is modified chemically. However, a greater array of methods to prepare four-memebered rings would allow for access to broader structural diversity of this class of antibiotics. Other examples of naturally occurring molecules which prominently feature four-membered rings include certain opiate alkaloids. These chemical species can be isolated from marine sponges and various plants which exhibit antimicrobial, antibacterial, and anticancer activity (Figure 2.2).[2]

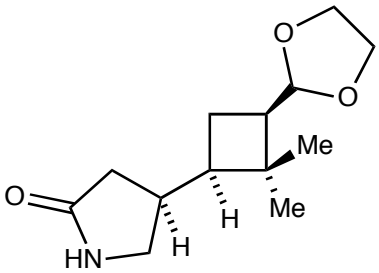


Carboplatin - anticancer drug

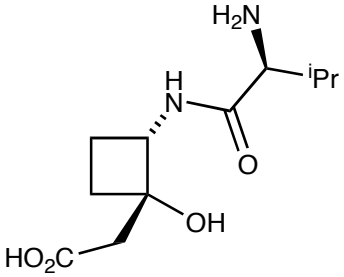


Penicillin core - antibacterial drug

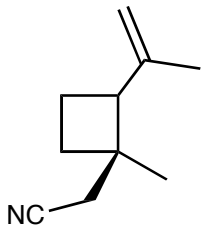
Figure 2.1. Therapeutic agents containing a cyclobutane moeity.



GABA-analog



Antibiotic activity



Anticancer activity

Figure 2.2. Naturally occuring plant and marine sponge opiate alkaloids.

Light-mediated [2π+2π] cycloadditions have been observed in nature. One example is the chemical modification of DNA by UV light to form thymidine dimers, resulting in cyclobutane-containing nucleic acids. Despite the body's ability to reverse damage, thymidine dimer formation is still another important example of naturally occurring four-membered ring-containing biomolecules (Figure 2.3).[3] Another well-known light-mediated cycloaddition is the formation of truxillic acid from cinnamic acid.[4] Truxillic acid and its derivatives have been identified as minor constituents of crude oil of coco. A variety of truxillic acid derivatives are depicted in Figure 2.4.[5,6]

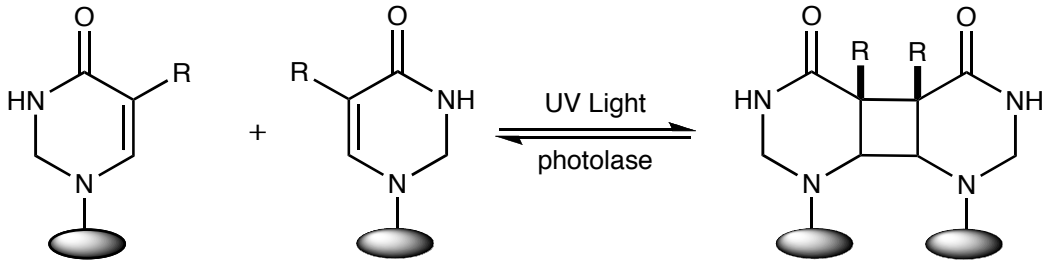


Figure 2.3. Photodimerization of DNA subunits.

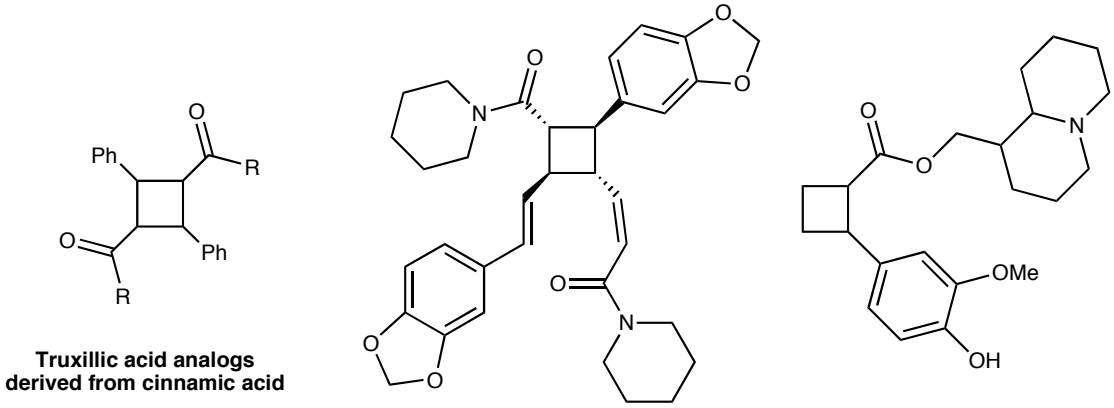


Figure 2.4. Truxillic acid derivatives.

Given the previously mentioned applications, the chemical synthesis of cyclobutane derivatives is somewhat limited and deserves greater exploration. Although the dimerization of ethylene is a thermodynamically favored reaction, it is thermally forbidden, requiring high temperatures or light to facilitate completion. However, there are ways that this limitation can be overcome. Some catalysts have shown the ability to facilitate [2π+2π] cycloadditions. With activated alkenes, alkynes, and other highly reactive molecules, [2π+2π] reactions can occur at less forcing conditions even in the absence of catalysts. One such example is the reaction between

aldoketenes and imines in refluxing benzene which resulted in the formation of azetidinones in good yield (Figure 2.5).[7,8]

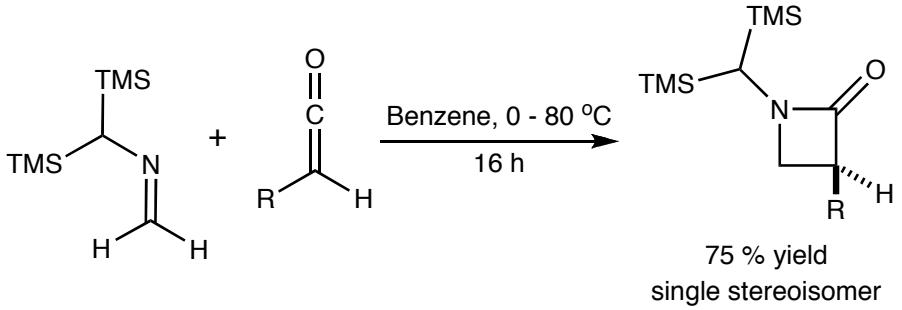


Figure 2.5. Thermal [2π+2π] reaction under mild conditions.

An intramolecular variant of activated double bonds undergoing [2π+2π] reactions is highlighted in the work of Holcomb, where various ketene-allene cycloadditions were observed.[9] The reaction conditions were non-photochemical, requiring only refluxing acetonitrile or benzene to isolate either [3.1.1]-bicycloheptanones or [3.2.0]-bicycloheptanones in good to moderate yields. The larger the allenyl-R group, the more favored the [3.2.1]-product became (Figure 2.6). Another recent example of a non-photochemical [2π+2π] reaction of activated π-bonds was reported by Hsung and coworkers[10]. Benzyne generated in situ from *o*-(trimethylsilyl)phenyl triflate and cesium fluoride reacted with enamides to form benzocyclobutanes in good yields (Figure 2.7).

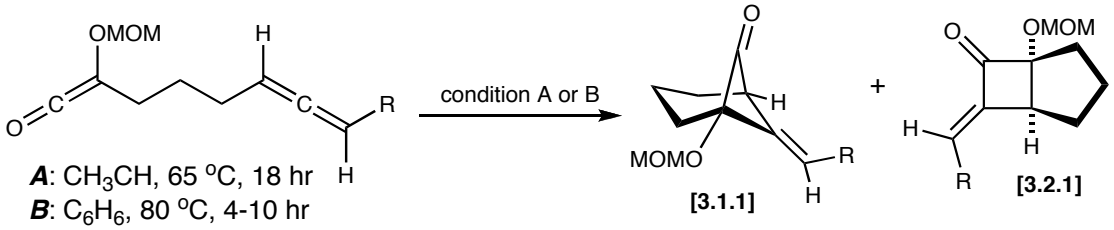


Figure 2.6. Intramolecular reaction between ketene-allenes.

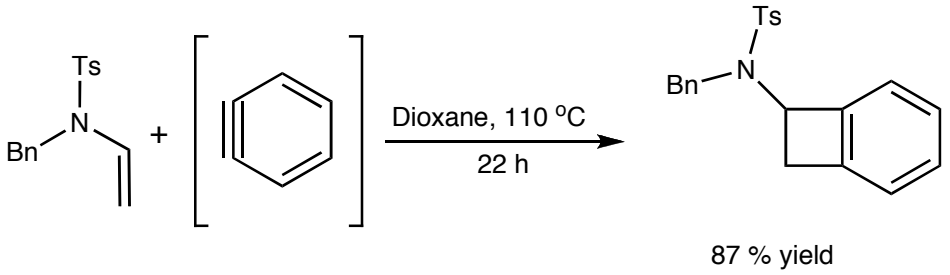


Figure 2.7. Reaction between enamide and in-situ generated benzyne.

There are a few recent literature examples of cyclobutenone/butanol formation catalyzed and mediated by transition metals. Toste and coworkers have reported the preparation of cyclobutenones using two distinct gold-catalyzed approaches. The first employs alkynylcyclopropanols as the starting material with $(p\text{-}CF_3\text{-}C_6H_4)_3PAuCl$ as a catalyst and silver hexafluoroantimonate as an activator, resulting in excellent yields of cyclobutenones at room temperature.[11] The second method occurs via the gold-catalyzed isomerization of allenylcyclopropanols to vinyl cyclobutanones (Figure 2.8).[12]

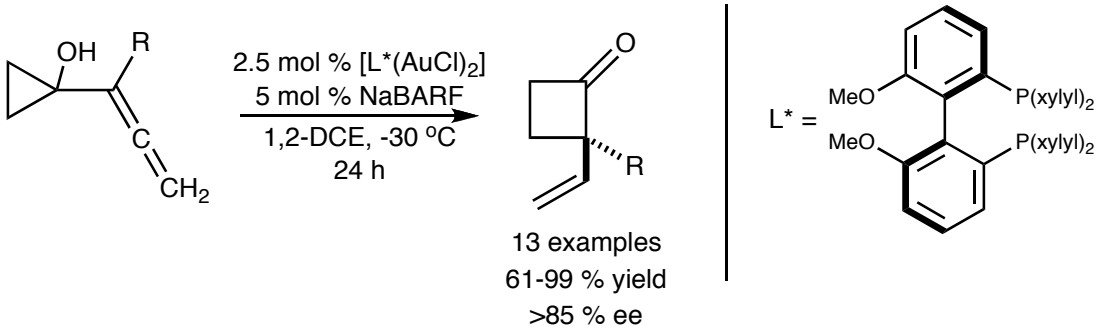


Figure 2.8. Preparation of vinyl-cyclobutanones from allenylcyclopropanols using gold-catalysis.

Cyclobutanols have also been prepared in good to moderate yields from 1,1,1-trichloroalkanes and enones by the tandem mediation of chromium chloride and copper cyanide at room temperature in THF (Figure 2.9). This example and reports

from the Toste lab highlight the use of transition metals to overcome the thermal disallowance of cyclobutane formation from alkenes.[13]

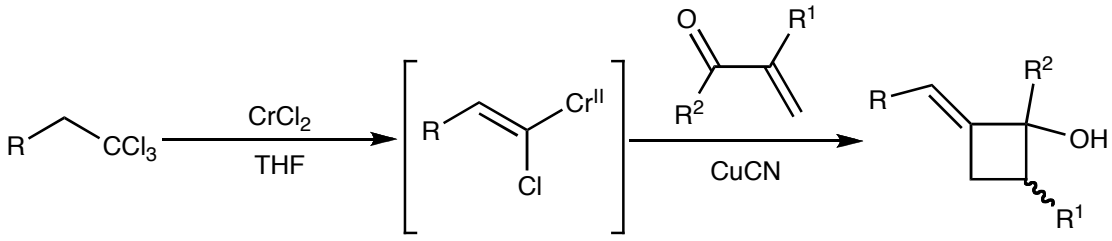
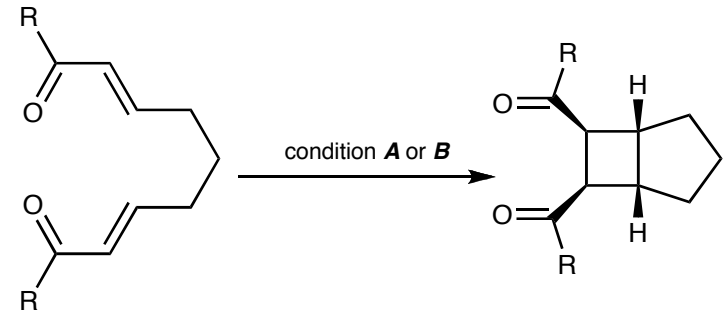


Figure 2.9. Chromium and copper mediated cyclobutanol formation.

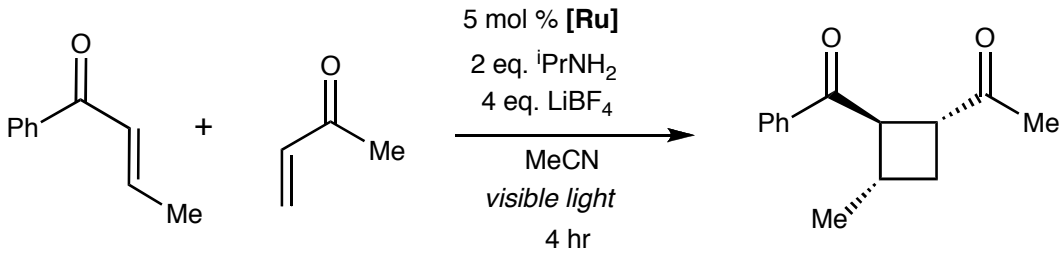
Activated bis(enones) have been converted to their [3.2.0]bicycloheptane derivatives by transition metals under various conditions (Figure 2.10). All of these conditions revolve around an initial one-electron reduction of the substrate. Krische and coworkers have shown that this reaction can be catalyzed by reduced $(dpm)_2Co$ (dpm = 2,2,6,6,-tetramethyl-heptane-3,5-dionate) or by 25 mol % Me_2CuLi.[14] These two distinct experimental conditions imply that this reaction proceeds via one-electron reduction of the substrate. Krische and coworkers provided further support for this mechanism by the addition of the stoichiometric reductant sodium chrysene ($Na[C_{18}H_{12}]$), which facilitated the conversion of biseneones to the [3.2.0]bicycloheptyl motif.[15] The activated bis(enones) undergo a facile one-electron reduction and cyclization to yield a cyclopentyl radical anion, followed by subsequent carbon-carbon bond formation resulting in the [3.2.0]bicycloheptane core. Yoon et al have employed $[Ru(bpy)_3]^{2+}$ as a catalyst under ambient light. Under these conditions, bis(enones) competently underwent [2π+2π] cycloisomerization to form bicyclic products with excellent yields and good diastereoselectivity.[16] Subsequently, Yoon's methodology was also extended to intermolecular examples where two different

acyclic enones could be dimerized to form cyclobutanes in moderate to good yields with good diastereoselectivity (Figure 2.11).[17]



Condition ***A*** (Krische): [Na(chrysene)]
Condition ***B*** (Yoon): 5 mol % $Ru(bipy)_3Cl_2$

Figure 2.10. [2π+2π] reaction of bis(enone) to form [3.2.0]bicycloheptane derivative.



[Ru] = $Ru(bipy)_3Cl_2$

84 % yield, >10:1 d.r.

Figure 2.11. Light-mediated, ruthenium-catalyzed intermolecular [2π+2π] reaction.

Unactivated 1,6-dienes can be cyclized in the presence of various copper salts and light. Copper(I) halides, such as chloride and bromide, are efficient catalysts for the preparation of [3.2.0]-bicycloheptanes, but Cu(I)OTf is a superior catalyst as a result of the non-coordinating nature of the counterion. For this reaction to be effective, the substrate must have a coordinating group, particularly an alcohol functionality or an ether functionality.[18] These ancillary groups allow for

precoordination of the copper catalyst with the diene, in the stoichiometry of two olefins to one metal center.

Previously it was recognized that (^{iPr}PDI)Fe(N_2)$_2$ ((^{R}PDI = 2,6-(2',6'-R_2-C_6H_3N=CMe)$_2C_5H_3N$; R= iPr, Me) was a competent catalyst for the cycloisomerization of unactivated 1,6-dienes.[19] The original communication primarily reported the complete cycloisomerization of a few protected diallyl amines and some commercially available dienes (e.g., 1,6-heptadiene and diethyl diallyl malonate) to the [2π+2π] bicyclic product A. The stereochemistry of the bridgehead hydrogens was determined as *cis* with respect to each other (Figure 2.12), which was also the favored configuration as determined by DFT calculations. This methodology is noteworthy because it is the only example of a non-photochemical (thermal) metal-catalyzed [2π+2π] cyclization reaction of unactivated olefins.

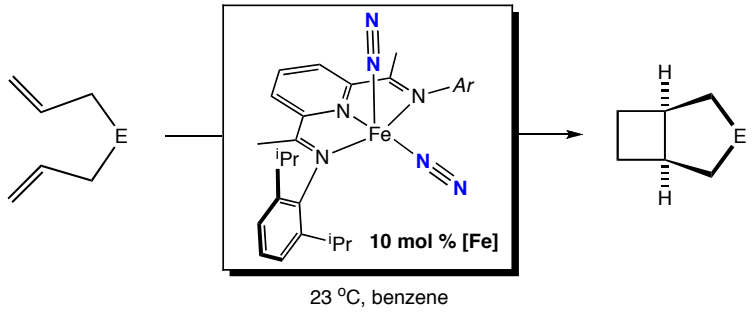


Figure 2.12. Iron-catalyzed cycloisomerization of 1,6-heptadienes.

In the mechanistic hypothesis for this iron-catalyzed transformation, it is purported to proceed through an iron-metallocyclic intermediate which allows for smooth reductive elimination. This reaction is possible because the redox activity of the PDI ligand allows for the iron center to remain in the ferrous (+2) oxidation state throughout the catalytic cycle. It is this ability of the PDI ligand to accept electrons

and then lose electrons that allows this reaction to proceed catalytically without loss of iron metal (Figure 2.13).

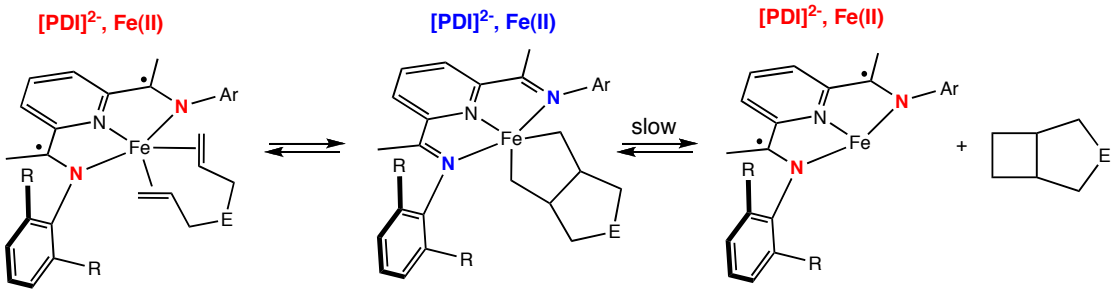


Figure 2.13. Proposed mechanism of [2π+2π] iron-catalyzed reaction.

The purpose of this chapter is to build upon the preliminary, yet unique results that were reported in the original communication. With the recent development of new bis(imino)pyridine iron catalysts in our lab, the potential for exploration of this reaction has increased greatly. Moreover, the diastereoselectivity and chemoselectivity of the reaction will be investigated and extended to practical bench-top and standard Schlenk techniques.

2.3 Results

Exploration of the scope of Fe-catalyzed [2π+2π] 1,6-diene cycloaddition.

Invoking the intermediacy of a metallobicycle in the Fe-catalyzed [2π+2π] reaction, a notable effect on the rate of reaction should be observed depending upon the steric demand of the E-group (Figure 2.12). The Thorpe-Ingold[20] effects stated that the rate of a cyclization reaction increases as the steric demand around a quaternary carbon increases, thereby forcing the reacting partners (dienes, in this case) into closer proximity. Thus, with increasing steric bulk a rate acceleration should be observed.

Exploration of the Thorpe-Ingold Effect. Diethyl diallyl malonate was easily decarboxylated in presence of lithium chloride and water in refluxing DMSO. Exposing the resultant product, diallyl ethyl acetate, to 5 mol % (^{iPr}PDI)Fe(N_2)$_2$ resulted in formation of the expected [2π+2π] product in 500 minutes (turnover frequency = 2.4 hr^{-1}, > 95 % conversion by ^{1}H NMR). Previously, 1,6-heptadiene was cleanly converted to [3.2.0]bicycloheptane and diethyl diallyl malonate (DEDAM) was converted to diethyl [3.2.0]bicycloheptane-3,3-dicarboxylate in benzene using 10 mol % (^{iPr}PDI)Fe(N_2)$_2$.[19] In this study, 1,6-heptadiene and DEDAM were exposed to 5 mol % (^{iPr}PDI)Fe(N_2)$_2$ and, monitoring the reaction to > 95 % conversion by ^{1}H NMR, the former substrate was complete in 667 minutes and the latter substrate was complete in 300 minutes. The turnover frequencies in Figure 2.14 clearly highlight the effect of increased steric demand on the rate of cyclization.

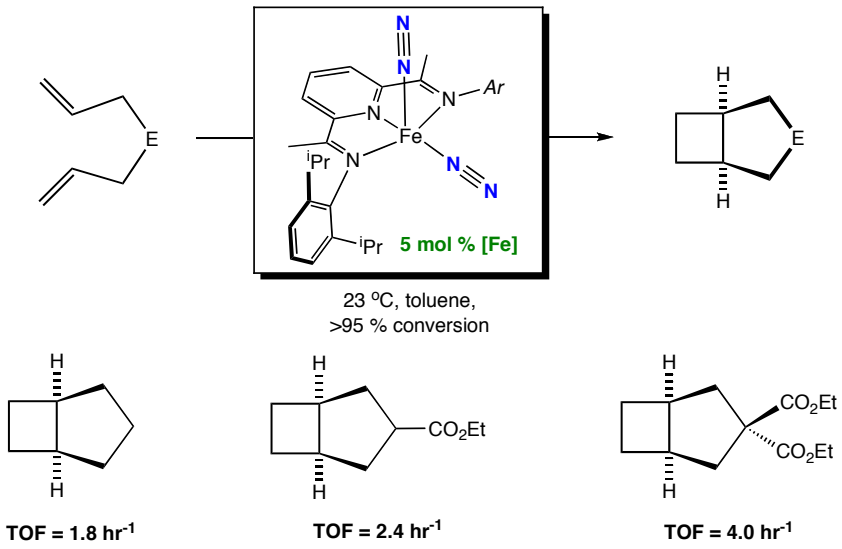


Figure 2.14. Measuring the Thorpe-Ingold effect for (^{iPr}PDI)Fe(N_2)$_2$-catalyzed [2π+2π] cyclization.

Protected diallylamines. Various substituted diallyl amines were prepared by protection of diallylamine in the presence of base or by bisallylation of the primary amine. The yields for the preparation of substrates were good to moderate.[21] Protected diallylamines were all cleanly converted into the expected [3.2.0]-bicycloheptane derivatives in the presence of (^{iPr}PDI)Fe(N_2)$_2$ in benzene or toluene with 5 mol % (^{iPr}PDI)Fe(N_2)$_2$. The substrates that were more sterically hindered underwent the reaction more quickly (e.g., ^{t}Bu[19] is faster than Cy) (Figure 2.15). Diallyl aniline cyclized faster than the para-fluoro substituted analogue, implying that the fluoro-analogue may by inhibited by product formation.

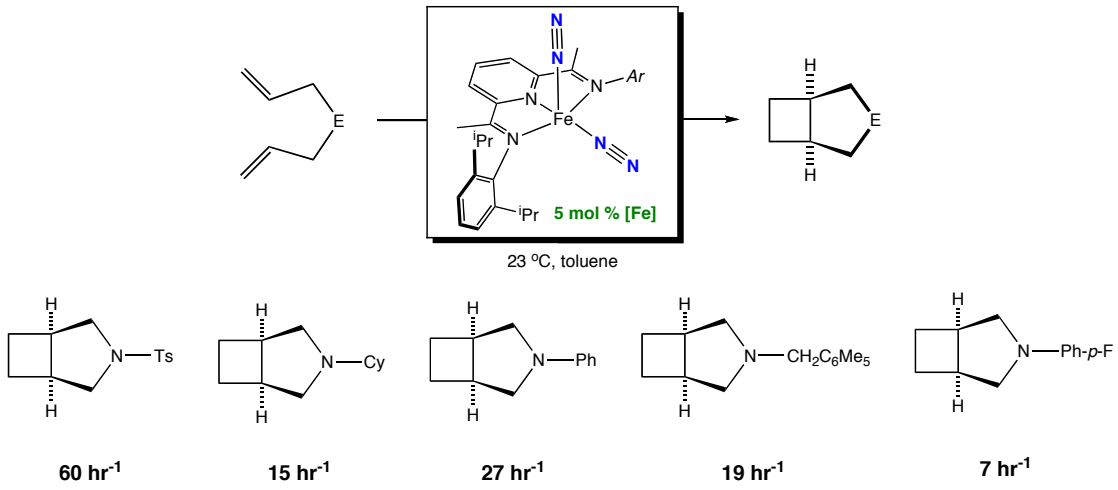
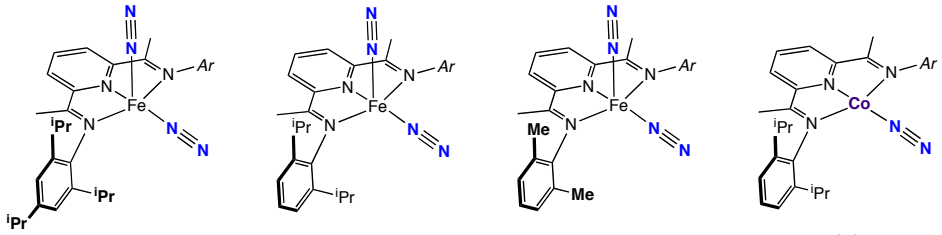


Figure 2.15. Iron-catalyzed [2π+2π] cycloadditions of protected diallylamines.

Evaluation of catalyst performance. Various substituted-PDI iron and cobalt compounds have been prepared in our lab and the labs of other researchers. These modifications to the metal compounds represented both electronic and steric variations that could potentially give rise to different reactivity and activity. The activity of three additional catalysts ((^{iPr}PDI)Co(N_2)$_2$, (^{trips}PDI)Fe(N_2)$_2$, and [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2)) were explored when 5 mol % catalyst was exposed to *N,N,*-diallyltosylamine.

Reactions were monitored by ^{1}H NMR spectroscopy for >95% consumption of starting diene. Diallyltosylamine was chosen as the model substrate to determine the effect of catalyst variation on the rate of the reaction because of its ease of preparation and facile reactivity. When diallyltosylamine and catalytic (^{iPr}PDI)Fe(N_2)$_2$ were combined in benzene, the solution immediately turned red. After five minutes the solution turned green, indicating that the reaction was complete and diallyltosylamine was converted to N-tosyl-3-aza[3.2.0]bicycloheptane (Figure 2.16). When the less hindered iron-catalyst [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) was exposed to twenty equivalents of diallyltosylamine, two distinct products were observed. The first, the anticipated [2π+2π] cyclization product (**A)**, and the second unexpected product, *N*-tosyl-3-methylene-4-methylpyrrolidine **(B)**, were formed in a 3:7 ratio as determined by ^{1}H NMR spectroscopy in deteurated benzene. Exposing twenty equivalents of diallyltosylamine in deuterated benzene to the less reducing[22] (^{iPr}PDI)Co(N_2)$_2$ resulted in the formation of an equimolar mixture of products **(A)** and **(B)** as measured by ^{1}H NMR spectroscopy. Finally, the new bis(imino)pyridine iron dinitrogen compound (^{trips}PDI)Fe(N_2)$_2$ (trips = 2',4',6'-triisopropyl) was prepared by sodium-amalgam reduction of the corresponding iron-dibromide. This more reducing and sterically hindered catalyst was mixed with twenty equivalents of diallytosylamine in deuterated benzene with the observation of only product **(A)**. For each catalyst individually, the time to reach 95 % consumption was monitored by ^{1}H NMR, and converted to a turnover frequency. The results of these measurements are reported in Figure 2.16. The more sterically hindered catalysts exhibited greater selectivity for the [2π+2π] product as specifically observed in the cases of (^{iPr}PDI)Fe(N_2)$_2$ and (^{trips}PDI)Fe(N_2)$_2$. Additionally these two catalysts were more active, reaching complete conversion in under twenty minutes (as monitored by ^{1}H NMR spectroscopy). A loss of activity

and selectivity was observed with both (^{iPr}PDI)Co(N_2)$_2$ and [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2). A summary of results is given in Figure 2.16.



TOF (hr^{-1}):	60	60	0.4	0.2
A:B	>19:1	>19:1	3:7	1:1

Figure 2.16. Catalyst scope for cyclization of diallyltosylamine.

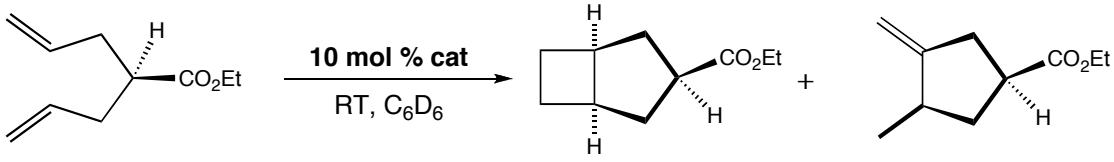
Given the differences in selectivity and activity observed in the Fe-catalyzed cyclization of diallyltosylamine, other substrates were tested. In the case of diallyl aniline, [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) showed the worst selectivity with a product ratio of 56 % **A** to 44 % **B**. Both isopropyl-substituted PDI catalysts showed complete selectivity for the [2π+2π] product; however, the cobalt congener was 70 times slower than the iron catalyst.

When 1,6-heptadienes substituted with carbons at the four-position were employed, (^{iPr}PDI)Co(N_2) produced no turnover with extended reaction times (two days) at room temperature. However, as the temperature was increased to 60 ˚C, the selectivity for the [2π+2π] reaction increased. 1,6-Heptadiene cleanly cyclized to the [3.2.0]bicycloheptane in the presence of both catalytic amounts of (^{iPr}PDI)Fe(N_2)$_2$ and (^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2); however, the isopropyl-substituted catalyst was about three times faster.

Diallyl ethyl acetate, when exposed to 10 mol % of (^{iPr}PDI)Fe(N_2)$_2$, was cleanly converted to one diastereomer with the ester functionality *trans* to the bridgehead hydrogens.[23] Complete diastereoselectivity was also observed when

(^{trips}PDI)Fe(N_2)$_2$ and [(^{Me}PDI)Fe(N_2)]-μ-(N_2) were employed as the catalyst. However, in the ^{Me}PDI catalytic reactions, a slight loss of selectivity was noted because the exo-methylene product (**B**) was formed in 13% yield, though only as one diastereomer (Table 2.1). Higher loadings of catalyst were employed in the study of the reactivity of diallyl ethyl acetate because of the propensity of bis(imino)pyridine compounds to cleave ester functionalities[24] and because of their susceptibility to protonolysis by acidic compounds.

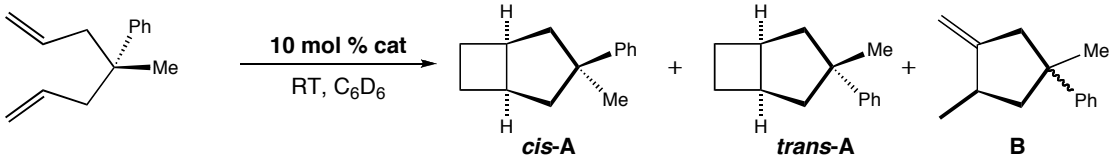
Table 2.1. Cycloisomerization of diallyl ethyl acetate by various catalysts.



			A	B
Catalyst	Time (hr)	TOF (hr^{-1})	% Conv. A (% Conv. B)	A isomer ratio (B isomer ratio)
(^{iPr}PDI)Fe(N_2)$_2$	8	2.4	>95 %	>19:1
(^{trips}PDI)Fe(N_2)$_2$	5	3.6	>95 %	>19:1
[(^{Me}PDI)Fe(N_2)]$_2$	12	1.7	87%(13%)	>19:1 (>19:1)
(^{iPr}PDI)Co(N_2)	18	-	<5%	-

When 4-methyl-4-phenyl-1,6-heptadiene and diallyl ethyl acetate were exposed to all four catalysts, (^{trips}PDI)Fe(N_2)$_2$ and (^{iPr}PDI)Fe(N_2)$_2$ showed the best activities and best selectivities for [2π+2π] product formation. Additionally, (^{trips}PDI)Fe(N_2)$_2$ showed a greater diastereoselectivity than (^{iPr}PDI)Fe(N_2)$_2$ for product ***cis*-A** (Table 2.2), likely because the small substituent (hydrogen or methyl) is oriented on the same face of the bicycle as the bridgehead hydrogens.

Table 2.2. Cycloisomerization of 1,1-diallyl-1-phenylethane by various catalysts.



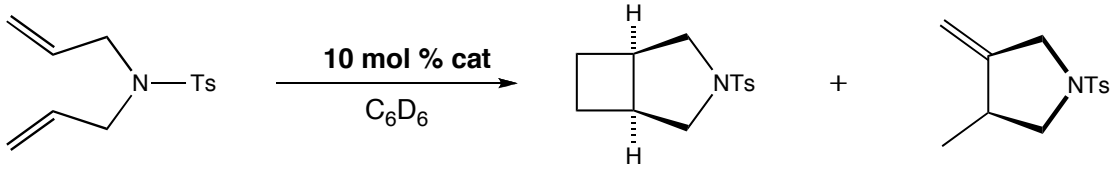
Catalyst	Time (hr)	TOF (hr-1)	% Conv. A (% Conv. B)	A isomer ratio (B isomer ratio)
$(^{iPr}PDI)Fe(N_2)_2$	3	4.6	>95 %	3:1
$(^{trips}PDI)Fe(N_2)_2$	2.2	3.4	>95 %	2:1
$[(^{Me}PDI)Fe(N_2)]_2$	25	0.4	57%(43%)	2:1 (3:2)
$(^{iPr}PDI)Co(N_2)$	50	0.2	>95 %	1.6:1

Temperature effects on product ratios. Because diallyl ethyl acetate was not converted to either the expected [2π+2π] product or the exo-methylene-cyclopentane in the presence of $(^{iPr}PDI)Co(N_2)$ at room temperature, and because diallyl tosylamine showed a different product distribution depending upon the catalyst, the effect of temperature was measured on the product ratio. The two model substrates chosen for this study were diallyl tosylamine and 1,1-diallyl-1-phenylethane. Higher catalyst loadings (10 mol % as compared to 5 mol %) were employed because the stability of reduced iron and reduced cobalt compounds tends to decrease with increasing temperature (as evidenced by the observed formation of $(^{iPr}PDI)_2Fe$ from $(^{iPr}PDI)Fe(N_2)_2$ in refluxing benzene)[25].

Exposing 10 equivalents of diallyltosyl amine to both $(^{iPr}PDI)Fe(N_2)_2$ and $(^{trips}PDI)Fe(N_2)_2$ facilitated the exclusive formation of product **A** at room temperature, so the reaction temperature was not changed. However, in the case of $(^{iPr}PDI)Co(N_2)_2$ and $[(^{Me}PDI)Fe(N_2)]_2$-μ-(N_2), the reactions were much more sluggish at room temperature, so the reaction temperature was increased. As the temperature was increased, the rate of the reaction increased, and the ratio of products of **A**:**B** also changed. For cobalt, the [2π+2π] product became the major product at 45 °C with a

ratio of 68 % **A** to 32% **B**. As the temperature was increased to 65 °C and finally, 100 °C, **A** became essentially the only product (~20:1 **A**:**B** as measured by ^{1}H NMR) (Table 2.3). When 10 mol % [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) and diallyltosylamine were subjected to elevated reaction temperatures, the product ratio of **A**:**B** increased from 3:7 (at room temperature) to about 3:2 (at 100 °C). However at, 100 °C, the reaction was measured by ^{1}H NMR to have achieved only 80 % completion, likely a result of catalyst decomposition (Table 2.3).

Table 2.3. Temperature effects on cycloisomerization of diallyltosylamine.



A **B**

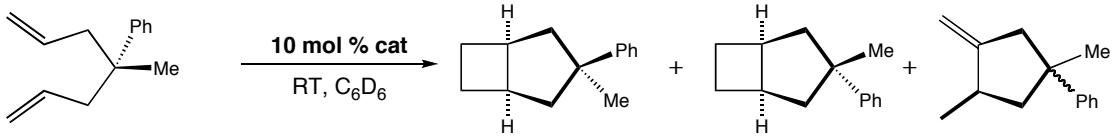
Catalyst	Time[a] (hr)	Temp. (°C)	TOF (hr^{-1})	Conv. (%)	% A	% B
^{iPr}PDIFe(N_2)$_2$	>0.17	23	>60.	>95	>95	-
(^{trips}PDI)Fe(N_2)$_2$	>0.17	23	>60.	>95	>95	-
[(^{Me}PDI)Fe(N_2)]$_2$	6	23	1.7	>95	29	71
[(^{Me}PD^{I})Fe(N_2)]$_2$	1	45	6.8	68	41	59
	1.75		5.7	>95	38	62
[(^{Me}PDI)Fe(N_2)]$_2$	1	65	>10	>95	48	52
[(^{Me}PDI)Fe(N_2)]$_2$	0.75	100	10.6	80	60	40
(^{iPr}PDI)Co(N_2)	36	23	1.1	>95	50	50
(^{iPr}PDI)Co(N_2)	1.25	45	5.3	66	58	42
	2.5		4.0	93	68	32
(^{iPr}PDI)Co(N_2)	1.25	65	>8.0	>95	95	5
(^{iPr}PDI)Co(N_2)	1.25	100	>8.0	>95	>95	<5

[a]Time measured to reach 95 % conversion as measured by ^{1}H NMR.

A similar temperature study was undertaken with the 1,1-diallyl-1-phenylethane substrate. The rate of the reaction of 1,1-diallyl-1-phenylethane with

(^{iPr}PDI)Fe(N_2)$_2$ increased with increasing temperature, but none of the exomethylene product was formed. Only a slight variation in the diastereomeric ratio was observed. Exclusive formation of the [2π+2π] cyclization product was observed using the cobalt catalyst, but only at elevated temperature. A comparison of these results with those of other catalyst variants is shown in Table 2.4.

Table 2.4. Temperature effects on product ratio of 1,1-diallyl-1-phenylethane.



***cis*-A** ***trans*-A** **B**

Catalyst	Time[a] (hr)	Temp. (°C)	TOF (hr^{-1})	Conv. (%)	% A (DR)	% B (DR)
(^{iPr}PDI)Fe(N_2)$_2$	0.5	65	20	>95	>95 (2:1)	-
(^{iPr}PDI)Fe(N_2)$_2$	2.5	23	3.4	>95	>95 (2:1)	-
(^{iPr}PDI)Fe(N_2)$_2$	7.5	~ 5	0.4	30	>95:1 (2.5:1)	-
(^{trips}PDI)Fe(N_2)$_2$	2.0	23	4.5	>95	>95 (3.3:1)	-
[(^{Me}PDI)Fe(N_2)]$_2$	22	23	0.46	>95	57 (2:1)	43 (3:2)
(^{iPr}PDI)Co(N_2)	48	23	~ 0	<5	-	-
(^{iPr}PDI)Co(N_2)	50	65	0.2	>95	>95 (1.6:1)	-

[a]Time measured to reach 95 % conversion as measured by ^{1}H NMR.

Deuterium labeling studies. Diallyltosylamine-d_2 was prepared by deuterozirconation using deuterated Schwartz reagent[26] and bis(propargyl)tosylamine. The purpose of preparing the deuterated isotopologue was to probe for the presence of a rate-determining β-hydrogen elimination. Assuming the proposed intermediacy of the metallocycle resulting from the cyclization reaction between 1,6-dienes and (^{R}PDI)M fragments, two pathways to the product can be envisaged (Figure 2.17). The

first pathway is the facile, rate-determining reductive elimination from the metallocycle resulting in the observed bicyclic product. The second proposed pathway involves a (possibly) rate-determining β-hydrogen(deuterium) elimination resulting in a metal alkyl hydride, which would then undergo fast reductive elimination to form the observed exo-methylene product. If deuterium elimination were rate determining in the second proposed pathway, then the measured product ratio of bicycle to exomethylene products should be different when comparing the cyclization reaction of unlabeled diene and d_2-diene with bis(dinitrogen) metal complexes.

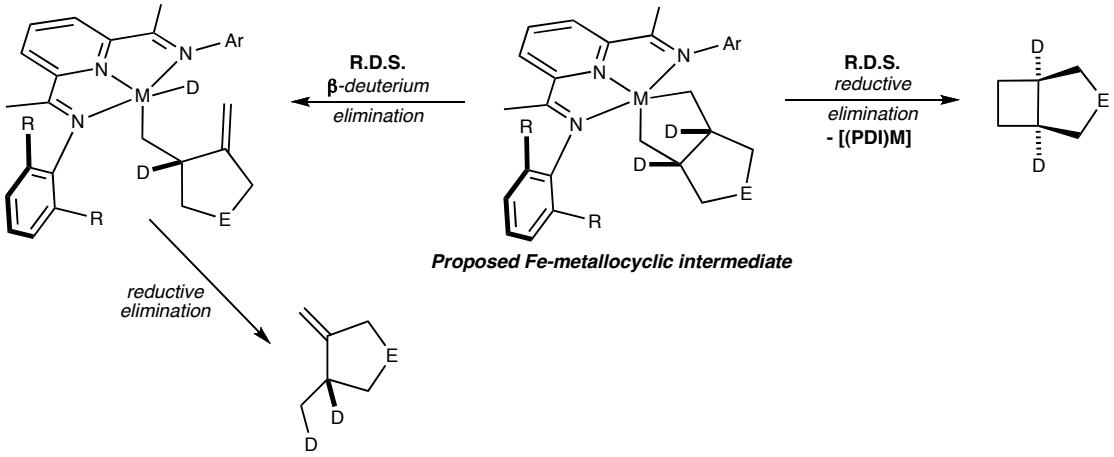


Figure 2.17. Proposed pathways for formation of observed cyclization products.

This deuterated substrate was subjected to 10 mol % [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2), and after one hour the starting material was completely consumed. Hydrolysis of the reaction and analysis by proton and deuterium NMR revealed that the product ratio was about 30 % [2π+2π] product to 70 % exo-methylene product. The [2π+2π] product was the d_2-isomer with incorporation into the bridgehead hydrogens, whereas the exo-methylene product was predominantly the d_1-isomer with incorporation into the methine. A small amount of deuterium had incorporated into the exo-methyl

group. Also, the deuterium NMR spectrum showed that incorporation into the methyl group of the aniline had also occurred (Figure 2.18).

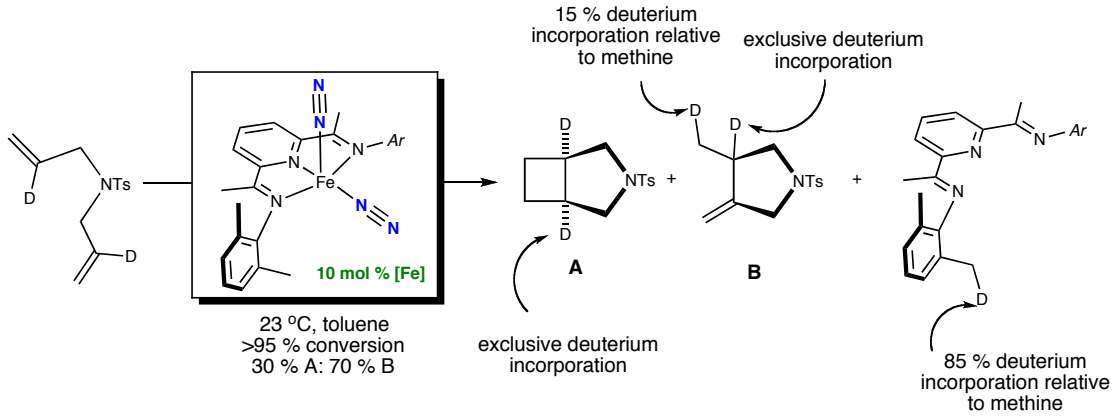
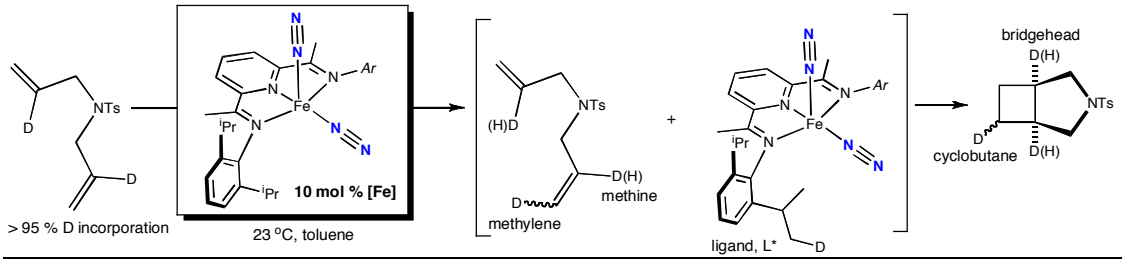


Figure 2.18. Results of catalytic reaction using d_2-diallyltosylamine.

A detailed examination of the reaction mixture revealed varying deuteration as the reaction proceeded. Scrambling of deuterium into the geminal positions of the substrate was observed in conjunction with ligand scrambling. Results are given in Table 2.5 below. It was also observed that the rate with the perproteo-substrate was comparable to that of the dideuterio-substrate.

Finally, the reaction was performed between deuterated catalyst ([(^{Me}PDI*)Fe(N_2)]$_2$-μ-(N_2), ^{Me}PDI* = d_{12}) and perproteo-substrate. As shown in Figure 2.19, the ratio of bicyclic product to exo-methylene product was nearly identical to that for the unlabeled catalyst, a strong indication that scrambling occurs after the rate-limiting step. Deuterium incorporation into each of these species and into free ligand was also observed.

Table 2.5. Scrambling ratios in deuterium labeling experiment.



Time (min)	% Conversion	Methine D: Methylene D	Bridgehead D: Cyclobutane D	% of Deuterium in Ligand
0	-	>19:1	-	0%
2	43.5	7.6:1	21:1	17.7%
4	61.0	5.3:1	16:1	20.4%
6	81.9	2.9:1	15:1	25.3%
10	>95	-	13:1	21.3%

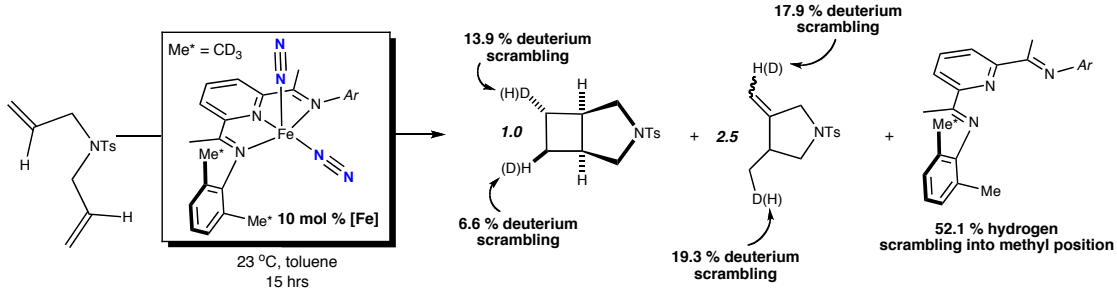


Figure 2.19. Results of catalytic reaction using [(^{Me}PDI*)Fe(N_2)]$_2$-μ-(N_2).

Evaluation of catalytic ability of redox-innocent iron-complexes for [2π+2π] reaction. Two other ligand scaffolds were also tested for [2π+2π] activity. The substrate chosen for this reactivity screen was *N,N*-diallyl-*t*-butylamine because it was the most reactive substrate when exposed to catalytic amounts of (^{iPr}PDI)Fe(N_2)$_2$. The first complex assayed for [2π+2π] activity was Danopoulous's reduced iron-dinitrogen compound.[27] Danopoulous's compound has a similar steric environment to (^{iPr}PDI)Fe(N_2)$_2$, has a more reducing ligand environment (based on a comparison of N_2 stretching frequencies), and is formally iron(0), but presumably it lacks the redox

activity of the bis(imino)pyridine ligand framework. Exposing twenty equivalents of *N,N*-diallyl-*t*-butylamine to Danopoulous's compound in benzene for twenty-four hours did not result in product formation when monitored by ^{1}H NMR (Figure 2.20). The second iron complex assayed for [2π+2π] activity was the bis(amido)pyridine-iron THF compound which was previously reported in our lab[28]. The complex is formally iron(II) and lacks the capacity for redox-activity, because of the diminished π-acidity of the dianionic ligand. When this Fe(II) complex was combined with 20 equivalents of *N,N*-diallyl-*t*-butylamine, no reaction was observed even after 24 hours in deuterated benzene as monitored by ^{1}H NMR (Figure 2.21).

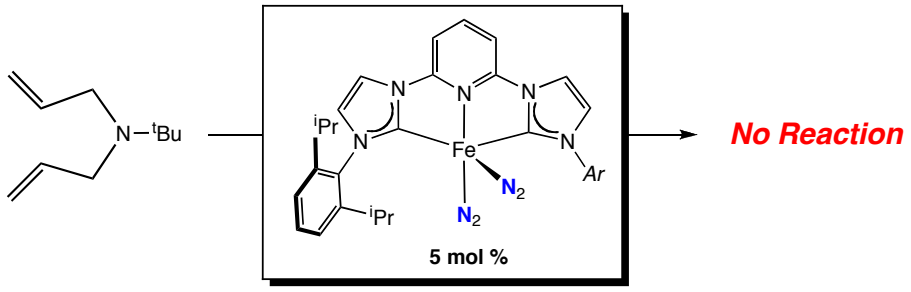


Figure 2.20. Addition of excess N,N-diallyl-*t*-butylamine to Danopoulous's reduced iron-dinitrogen compound.

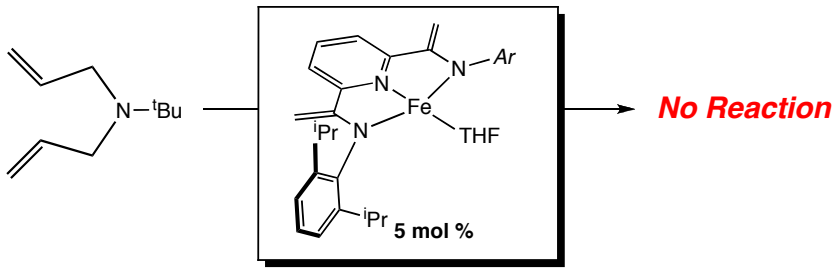


Figure 2.21. Addition of excess N,N-diallyl-*t*-butylamine to bis(amido)pyridine-iron THF compound.

Results of in situ catalyst generation. With the divergent reactivity of ^{Me}PDIFe, catalyst variation seemed like a logical extension to the [2π+2π] work in order to find a catalyst or conditions that would allow for complete conversion to the exo-methylene product **B**. Previously it had been shown that (^{iPr}PDI)$FeBr_2$, when reduced in situ with two equivalents of sodium triethylborohydride in the presence of excess diallyl-*t*-butylamine, catalyzed the [2π+2π] reaction[19]. Thus, a series of iron-dihalides with different PDI ligands were screened for catalytic activity when reduced with two equivalents of sodium triethyl borohydride (Figure 2.22). The substrate chosen for this screen was diallyl aniline because it could be present in the reaction prior to the addition of the reductant with minimal deleterious reactivity. All precatalysts that had methyl backbones and diisopropyl substitution on the aniline completely converted diallyl aniline to the [2π+2π] product. For the *para*-substituted trifluoromethyl group the slowest conversion was noted, whereas for the electron-rich *para*-dimethyl amino substituted PDI, the fastest rate was observed. Phenyl substitution off of the imine carbon severely slowed the reaction, as only 40 % of the starting material was converted to the expected [2π+2π] product after 40 hours.

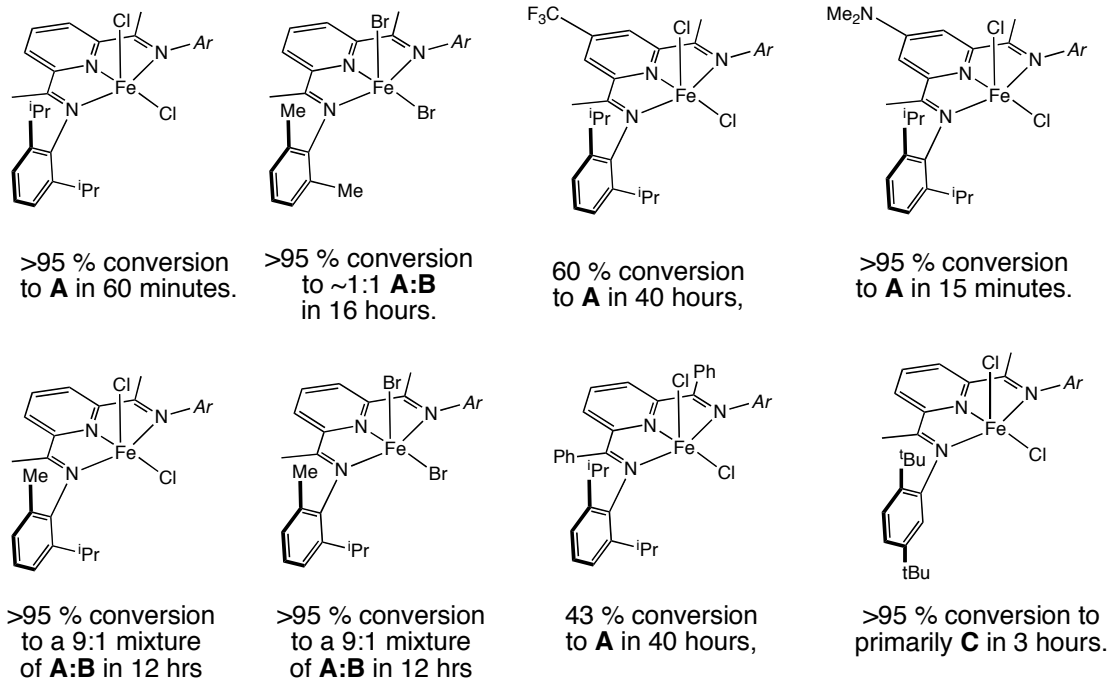


Figure 2.22. Results of active in situ generated catalytic reactions that consumed diallyl aniline [Fe]= 0.5 eq. (PDI)FeX_2 + 1 eq. $NaEt_3BH$.

For catalysts that had smaller substitution on the aniline (dimethyl, diethyl and methyl isopropyl), a mixture of [2π+2π] product and exo-methylene product was obtained. A comparison of (^{Me,iPr}PDI)$FeCl_2$ and (^{Me,iPr}PDI)$FeBr_2$ revealed that the dichloride gave a cleaner mixture of the same product ratio. (There was less evidence of olefin isomerization in the case of the dichloride reaction.) For ($^{2,5\text{-di-}t\text{-}Bu}$PDI)$FeCl_2$ only one product was observed; however, it was not the exo-methylene product **B,** but rather was the 3,4-dimethyl-dihydropyrrole **C.** Catalysts lacking sufficiently large substitution at the two- or six-positions or with ethoxides on the ligand backbone performed poorly as catalysts (Figure 2.23).

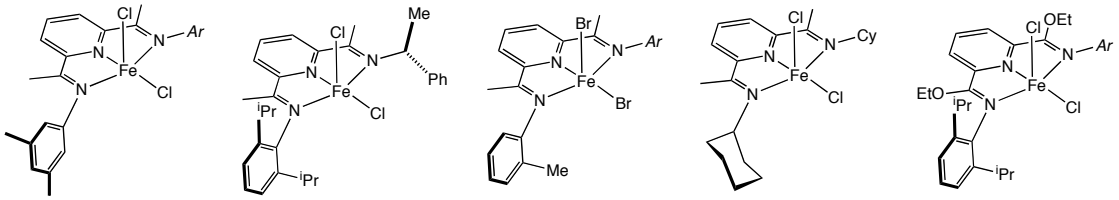


Figure 2.23. Catalysts that showed no reactivity toward diallylaniline.

When the in situ method was extended to a few other substrates, it was found that product **B** was the exclusively isolated product (except for recovered diallylaniline) (Figure 2.24). These conditions are exceedingly mild because the tosyl-protected amine is tolerated, an unexpected result given that reducing conditions (Li[naphthalenide)], sodium amide/ammonia)[29] are generally employed to remove a tosyl group.

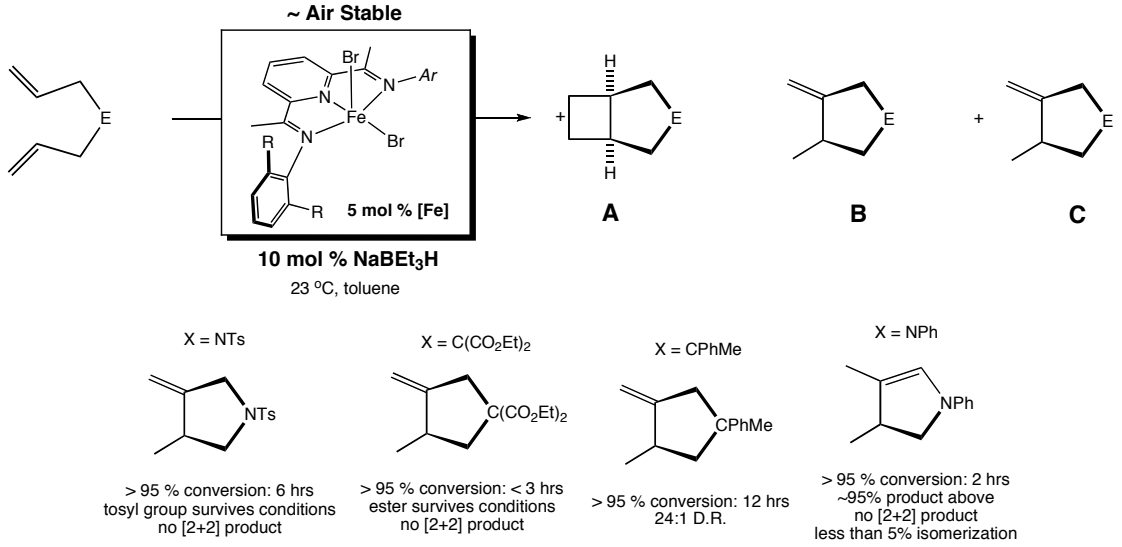


Figure 2.24. Substrate scope of in situ catalytic method.

2.4 Discussion.

When comparing the four catalysts employed for the various studies, a few general comments can be made. For the iron-based catalysts, the reaction occurred

faster than for the cobalt congener. This implies that the slow step is the reductive elimination from the metallocycle, because the more reducing catalysts (iron) should promote the faster reductive elimination. Also, the more sterically hindered catalysts facilitated faster reaction rates. This is evident in the loss of catalyst activity that was observed in comparing triisopropyl PDI, diisopropyl PDI, and dimethyl PDI. Holland and coworkers have shown that the addition of a *para*-isopropyl group increases the steric pressure around the metal center by pinching in the aryl rings.[30] A loss of product selectivity was also observed when smaller catalysts and less reducing catalysts were used, which probably results from the more open nature of the metallocycle intermediate. The openness of the complex would enable greater flexibility in the ring and allow the rate of β-hydrogen elimination to become competitive with (and in some cases faster than) reductive elimination. The most active and selective catalyst is therefore (^{trips}PDI)Fe(N_2)$_2$, but it is only slightly better than the original (^{iPr}PDI)Fe(N_2)$_2$.

It was originally proposed that the [2π+2π] reaction was faciliatated by the redox activity of the bis(imino)pyridine-iron system. In this metal-ligand framework, a ferrous oxidation state was proposed to be maintained throughout the entire catalytic cycle and electron transfer was assumed to occur within the ligand. The ability of bis(imino)pyridine ligands to accept and release two electrons would thus facilitate the proposed two-electron redox couple. Preliminary support for this hypothesis can be observed in the work of Grubbs and coworkers. The PDIFe fragment is isolobal with bisphosphinonickel, which was previously observed to promote the formation of cyclobutane from the decomposition of various bisphosphinonickel metallocycles (Figure 2.25).[31 32] Additionally, butenes and ethylene were observed as byproducts of thermal decomposition of the nickel metallacyclopentanes depending upon the phosphine substitution. In this work carried out by Grubbs in the late 1970s, it was

found that the rate of ethylene insertion was slower than the plating out of nickel black. This prevents turning over of the nickel-phosphine system.

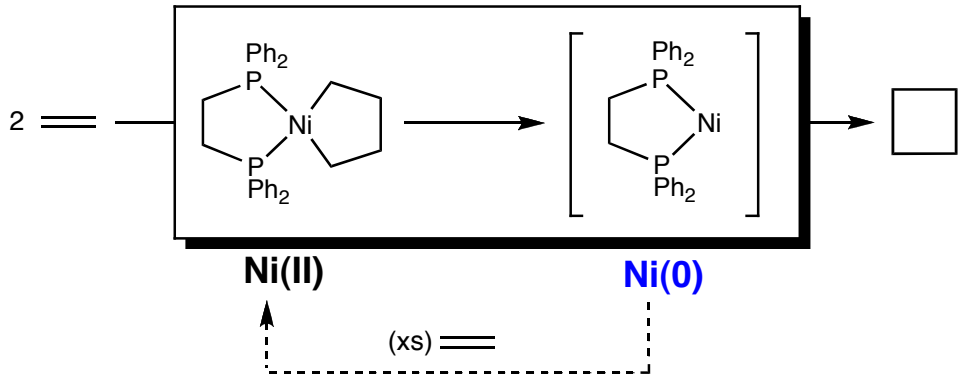


Figure 2.25. Oxidation state changes in [2π+2π] cyclization using nickel.

The reductive elimination from a series of bis(bipyridine)iron dialkyl complexes was studied by Kochi and coworkers. The decomposition mechanisms of the neutral, monocationic, and dicationic species were studied. The monocationic species could be electrochemically prepared from the neutral dialkyl and isolated as the perchlorate salt from THF. However, the dicationic species decomposed quickly when electrochemically prepared from the monocation. Reductive elimination from the neutral species was determined to proceed through dissociation of one bipyridine ligand followed by β-hydrogen elimination, to result in a mixture of alkanes and alkene, with the alkane always being formed in slight excess. Decomposition of $[(bipy)_2Fe^{III}R_2]^+$ occurred by homolytic cleavage of the iron alkyl bonds via a caged radical mechanism. In the case of $[(bipy)_2Fe^{III}Et_2][ClO_4]$, the ratio of products was determined to be 45 % butane, 48 % ethane, and 8 % ethylene. The same product distribution is observed in the photolysis of $Et_2N_2Et_2$, which is known to go by a caged

radical mechanism. Additionally, the fact that the product mixture from the decomposition of $[(bipy)_2Fe^{III}(CH_2)_4]^+$ was determined to contain both cyclobutane and butane, but no butene, gives support for a different mechanism of reductive elimination as compared to $(bipy)_2Fe^{II}(CH_2)_4$. Finally, the dications underwent a concerted reductive elimination, as evidenced by the clean formation of only diakyl products. Butane resulted from decomposition of $[(bipy)_2Fe^{IV}Et_2]^{2+}$, hexane resulted from the decomposition of $[(bipy)_2Fe^{IV}Pr_2]^{2+}$, and no pentane was observed during the crossover experiment. When $[(bipy)_2Fe^{IV}(CH_2)_4]^{2+}$ underwent thermolysis in the presence of bipyridine, only cyclobutane and $[(bipy)_3Fe]^{2+}$ were observed.

The iron-catalyzed formal [2π+2π] cyclization reaction explored in this chapter was hypothesized to proceed through an iron(II) metallocyclic intermediate. The redox changes that facilitated this transformation were purported to go through a two-electron transfer at the ligand, allowing the iron center to remain in the ferrous oxidation state. However, this model may need some refinement given recent work with bis(imino)pyridine iron dialkyls. (PDI)Fe(dialkyls), effective hydrosilylation catalysts, were determined to be high spin ferric (+3) complexes with a singly-reduced PDI ligand. In light of this determination, the intermediate iron metallocycle may be iron(III) with a mono reduced PDI ligand. Also, the work done by Kochi and coworkers on the reductive elmination of $(bipy)_2Fe^{III}$ dialkyl cations is consistent with the intermediacy of an iron(III), mono-reduced PDI metallocycle. Given that the Kochi dialkyl cations decompose via a radical mechanism and that both cyclobutane and 1-butene are observed in the decomposition, it can be expected that substantial radical character exists in the [2π+2π] reaction catalyzed by bis(imino)pyridine iron. The observation of deuterium into every position of the olefinic substrate as well as into the ligand is strongly suggestive of a highly unselective exchange process, which would be consistent with fast radical abstraction. The intermediacy of an iron(III)

intermediate could be further probed by the isolation of a cyclic PDIFe dialkyl. This could be achieved using the 2,3-disilylbutane fragment or by addition of highly electron deficient olefins to (^{iPr}PDI)Fe(N_2)$_2$, perhaps facilitating the formation of an isolable iron-metallocycle as in the work of Green and coworkers.[33,34,35]

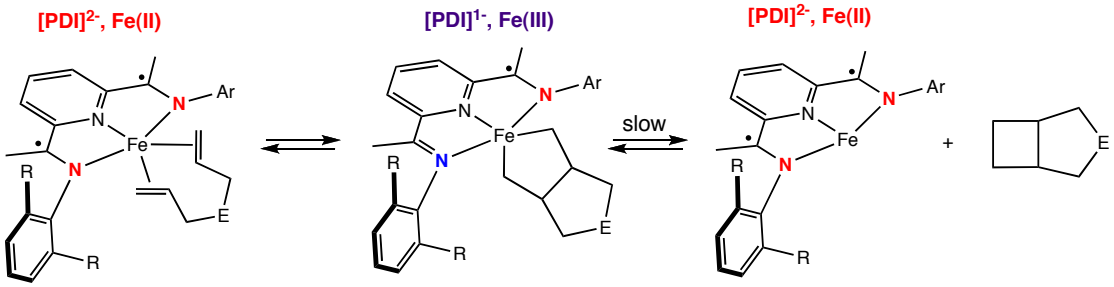


Figure 2.26. Modified mechanistic proposal for iron-catalyzed [2π+2π] reaction

In work previous work done by Amanda Bowman, it was discovered that exposing diallyl ether to 5 mol % (^{iPr}PDI)Co(N_2) facilitates the clean conversion to two products (Figure 2.26). The resultant product mixture is comprised of four equivalents of 3-oxo[3.20]bicycloheptane and one equivalent of 3-methylene-4-methyl-tetrahydrofuran. Based on the product ratio the favored pathway is reductive elimination, whereas the β-hydrogen elimination pathway is slower.

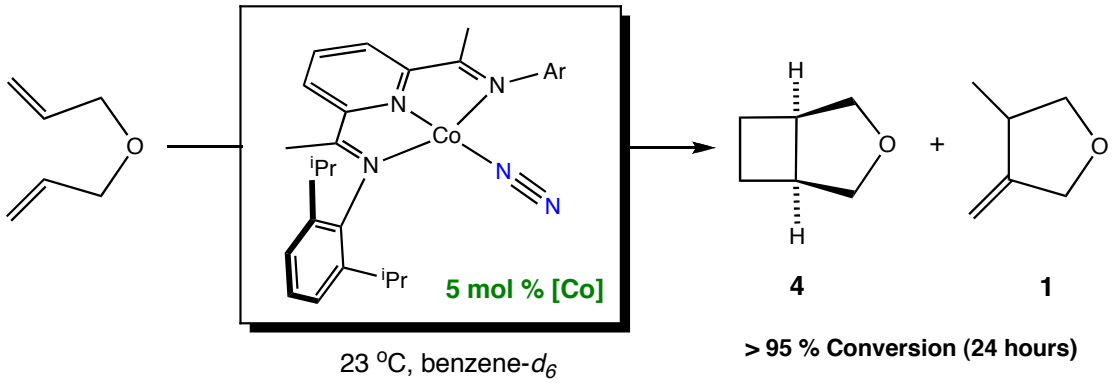


Figure 2.27. Cobalt-catalyzed cyclization of diallyl ether.

2.5 Conclusion

The unprecedented iron-catalyzed [2π+2π] cyclization reaction was further studied in the context of substrate scope and diastereoselectivity. The reaction methodology was extended to a series of protected diallylamines. The tosyl group and *p*-fluoroanilino protecting groups were tolerated under the reaction conditions. 2,2-Diallyl ethyl acetate and 4-methyl-4-phenyl-1,7-heptadiene were prepared and cleanly converted to the expected [3.2.0]-bicycloheptane. The former was observed to form only one diastereomer whereas the latter formed a 2:1 diastereomeric ratio. The favored diastereomer had the small substituent (hydrogen or methyl) oriented on the same face of the bicycle as the *cis*- bridgehead hydrogens. The selectivity and reactivity of four different bis(imino)pyridine metal nitrogen complexes were also assayed. The larger, more reducing complexes (^{trips}PDI)Fe(N_2)$_2$ and (^{iPr}PDI)Fe(N_2)$_2$ were observed to be more reactive and more selective for the bicycle. However, when smaller and less reducing catalysts ([(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) and (^{iPr}PDI)Co(N_2), respectively) were employed, diminished reactivity and the formation a secondary product was observed. The secondary product was identified to be an exo-methylene-methyl-cyclopentane (or pyrrolidine in case of amines). Higher temperatures increased the reaction rate and favored the formation of the bicycle irrespective of catalyst. The secondary product was hypothesized to arise from competitive β-hydrogen elimination from the proposed metallocyclic intermediate. Thus, the reaction mechanism was explored through a series of deuterium labeling experiments. Extensive isotopic scrambling from the deuterated substrate into the unlabeled ligand and from deuterated ligand into unlabeled substrate implied that the reaction mechanism was more complex that initially hypothesized. It is likely that radical abstraction reactions, arising from the presence of a ferric iron center in the proposed metallocycle, account for the extensive isotopic exchange observed in the reaction. Finally, the reaction

methodology was extended to an *in situ* method, allowing access to reduced bis(imino)pyridine iron complexes from treatment of their corresponding, air-stable iron dihalides with sodium triethylborohydride.

2.6 Experimental Procedures

General Considerations. All air- and moisture-sensitive manipulations were carried out using standard vacuum line, Schlenk and cannula techniques or in an MBraun inert atmosphere drybox containing an atmosphere of purified nitrogen. The MBraun drybox was equipped with a cold well designed for freezing samples in liquid nitrogen. Solvents for air- and moisture-sensitive manipulations were initially dried and deoxygenated using literature procedures.[36] Argon and dihydrogen gas were purchased from Airgas Incorporated and passed through a column containing manganese oxide supported on vermiculite and 4 Å molecular sieves before admission to the high vacuum line. Benzene-d_6 was purchased from Cambridge Isotope Laboratories and distilled from sodium metal under an atmosphere of argon and stored over 4 Å molecular sieves or sodium metal. $CDCl_3$ was purchased from Cambridge Isotope Laboratories and used as received. Diallyl sulfide was purchased from Acros and dried by passage though activated neutral alumina prior to use. The metal complexes (^{iPr}PDI)Fe(N_2)$_2$,[37] (^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) ,[38] (^{iPr}PDI)Co(N_2),[39] (^{iPr}pybox)FeNs$_2$,[40] and (^{iBu}pybox)FeNs$_2$[21] were prepared according to literature procedures. (^{trips}PDI)Fe(N_2)$_2$ was prepared in an analogous way to (^{iPr}PDI)Fe(N_2)$_2$. Diallyl sulfoxide was prepared from diallyl sulfide according to a previous report.[41] All other chemicals used were purchased from Acros or Aldrich and used as received.

^{1}H NMR spectra were recorded on Varian Mercury 300, Inova 400 and 500 spectrometers operating at 299.763, 399.780 and 500.62 MHz, respectively. All chemical shifts are reported relative to $SiMe_4$ using ^{1}H (residual) chemical shifts of the

solvent as a secondary standard. For paramagnetic molecules, the ^{1}H NMR data are reported with the chemical shift followed by the peak width at half height in Hertz or multiplicity, followed by integration value and where possible, peak assignment.

Mass spectra were acquired using a JEOL GCMate II mass spectrometer operating at 500 (LRMS) or 3000 (HRMS) resolving power (20% FWHM) in positive ion mode and an electron ionization (EI) potential of 70 eV. Samples were introduced via a GC inlet using an Agilent HP 6890N GC equipped with a 30 m (0.25 μ i.d.) HP-5ms capillary GC column. The carrier gas is helium with a flow rate of 1 mL/min. Samples were introduced into the GC using a split/splitless injector at 230 ˚C with a split ratio of 10:1 (HRMS) or 50:1 (LRMS).

N,N-Diallyltosylamine. Allylamine (1.25 g, 12.9 mmol) and triethylamine (2.18 g, 21.6 mmol) were added to 80 mL of methylene chloride. The reaction was cooled to in an ice bath. Tosyl chloride (2.45 g, 12.9 mmol) was added portionwise and the reaction was stirred at room temperature overnight. The reaction was quenched with 100 mL of saturated sodium bicarbonate. The product was extracted with methylene chloride (3x – 50 mL). The layers were separated and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure and the yellow oily reside was chromatographed on silica get eluting with hexane/metheylene chloride. The resulting clear, viscous oil (2.75 g) was identified as N,N-diallyltosylamine (83.1 % isolated yield). The spectral and physical properties are consistent with previously reported data.[42]

N,N-Diallylaniline. To a mixture of water/ethanol (32 mL/110 mL) was added aniline (2.88 g, 31.0 mmol) and sodium carbonate (3.40 g, 32.0 mmol). The solution was stirred for 20 minutes at room temperature. Allyl bromide (9.41 g, 78.0 mmol)

was added dropwise and the reaction was stirred at reflux for 16 hours. After 16 hours, the reaction was cooled an extracted with diethyl ether (3x – 100 mL) and the organic layer was dried over sodium sulfate. The solvent was evaporated and the yellow oily residue was chromatographed on neutral alumina and eluted with pentane/ether. The resulting clear, colorless oil (3.55 g) was identified as N,N-diallylaniline (63.6 % isolated yield). The spectral and physical properties were consistent with previously published data.[43]

N,N-Diallyl-2,3,4,5,6-pentamethylbenzylamine. This substrate was prepared by the allylation of *N*-(2,3,4,5,6-pentamethylbenzyl)prop-2-en-1-amine[44] using potassium carbonate in acetonitrile.

Diethyl Diallylmalonate. Sodium hydroxide (88.0 g, 2.2 mol) was dissolved in 175 mL of deionized water. Benzyl triethyl ammonium chloride (20.0 g, 88.0 mmol) was added to the basic solution and cooled in an ice bath. Diethyl malonate (14.2 g, 88.3 mmol) and allyl bromide (32.0 g, 264 mmol) were combined in a dropping funnel and added dropwise to the aqueous ammonium salt. The reaction was stirred for 16 hours during which time ambient temperature was reached. After 16 hours, the organic layer was extracted with diethyl ether (4x – 125 mL). The organic layer was dried over sodium sulfate and passed through a short silica plug. Evaporation of the solvent resulted in the isolation of 20.0 g of a very pale yellow oil identified as diethyl diallyl malonate **(**94.5 % isolated yield). The isolated product had spectral properties which were consistent with previously reported data.[45]

Ethyl 2,2-Diallylacetate. Combine diethyl diallyl malonate (3.70 g, 15.4 mmol), lithium chloride (1.43 g, 33.7 mmol), and water (308 mL, 17.1 mmol) in dimethyl

sulfoxide (30 mL). Reflux for six hours and then allow to cool to room temperature. Water (100 mL) was added to the reaction mixture and extracted with diethyl ether (3x – 100 mL). The combined organic layers were washed with water (5x – 15 mL), dried over magnesium sulfate, and filtered. The ether was evaporated to yield 1.95 g of a very pale yellow oil (75.3 % yield) identified as ethyl 2,2-diallylacetate. The physical and chemical properties of the compound were previously reported.[46]

Preparation of *N*,*N*-Diallyl-*p*-fluoro-aniline. *p*-Fluoroaniline (1.47, 13.2 mmol) was added to 20 mL of dimethylformamide. Potassium carbonate (5.40 g, 39.3 mmol) was added to the DMF solution and stirred for one hour. After stirring the reaction for one hour at room temperature, allyl bromide (4.00 g, 33.0 mmol) was added dropwise and the suspension was stirred overnight at room temperature. Water (100 mL) was added to dilute the reaction and extract with toluene (~150 mL). The combined organic layers were washed with water (5x – 10 mL) and brine (~20 mL). The toluene layer was then dried over magnesium sulfate and filtered. Concentration of the layer yielded a light red/brown oil, which was chromatographed on alumina using ether as an eluent. Evaporation of the solvent lead to isolation of a pale yellow oil identified as the expected product (7.1 mmol, 54 % isolated yield). Spectral and physical are consistent with previously published data.[47]

Preparation of *N*,*N*-Diallyl-cyclohexylamine. Cyclohexylamine (1.15 g, 11.6 mmol) and potassium carbonate (6.4 g, 46.4 mmol) were added to 30 mL of acetonitrile. The reaction was brought to reflux and potassium carbonate was added to the suspension dropwise through the reflux condensor. The reaction was heated overnight with precipitation of a white solid. The reaction was cooled and the acetonitrile was removed in vacuo. Water was added to the residue and extract with diethyl ether (4x –

50 mL). The ethereal layer was dried over magnesium sulfate and filter. Evaporation of the solvent and chromatography on alumina lead to isolation of 1.40 g of a light yellow oil identified as expected product (68 % yield). The spectral and physical properties were consistent with previously published reports.[42]

Preparation of 1-Phenyl-1,1,diallylethane. Added indium trichloride (432 mg, 1.95 mmol) to 30 mL of dry nitromethane. The reaction was stirred under argon for five minutes until solid $InCl_3$ dissolved. Trimethylsilyl chloride (2.0 g, 18.4 mmol) was dissolved in 4 mL of nitromethane and added to the indium chloride solution. Allyl trimethylsilane (4.5 g, 39.4 mmol) was dissolved in 8 mL of nitromethane and added to the reaction mixture. The temperature of the reaction was controlled with a water bath. Acetophenone (1.65 g, 13.4 mmol) was injected drop wise. The solution became yellow and eventually turned emerald green (and the solution released a slight amount of heat). The reaction was stirred at room temperature for 15 hours during which time it became red-brown and was then quenched with saturated sodium bicarbonate (100 mL). The organic product was isolated by extraction of the aqueous layer with diethyl ether (100 mL). The organic layer was dried over magnesium sulfate and filtered. Concentration and chromatographic purification on alumina yielded 2.0 g of the expected product (80 % isolated yield). Spectral characterization matches previously reported data.[48]

General Procedure for Catalytic Reactions with In Situ Generated Catalyst. All PDI iron dihalides were previously prepared and characterized from the free ligand and FeX_2 in THF under an inert atmosphere.[49] (PDI)FeX_2 (0.04 mmol) was dissolved in 4.34 mL toluene (5.0 g) in a scintillation vial in the dry box. A solution of *N,N*-diallylaniline (144 mg, 0.83 mmol) in toluene (1.25 mL, 1.1 g) was prepared and

added to the iron-dihalide toluene solution. The blue slurry was then placed at -35 °C (in the dry box freezer) for twenty minutes for 20 minutes. A toluene (0.867 mL, 1.0 g) solution of sodium triethyl borohydride (0.080 mL, 0.080 mmol, 1.0 M in toluene) was also prepared and stored in the dry box freezer for 20 minutes. After twenty minutes, the sodium triethyl borohydride solution was added dropwise to the blue suspension. The reaction (usually) turned red-brown and was allowed to warm to room temperature. The reaction was monitored as a function of time by ^{1}H NMR. Reaction times and conversions are listed in the results section.

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CHAPTER 3

BIS(IMINO)PYRIDINE IRON METALLOCYCLES: C-C BOND ACTIVATION AND CHARACTERIZATION OF INTERMEDIATES IN CYCLIZATION CATALYSIS.

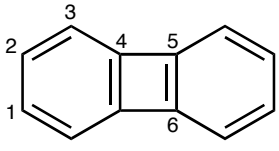
3.1 Abstract

A series of bis(imino)pyridine iron metallocycle compounds has been prepared by treatment of (^{iPr}PDI)Fe(N_2)$_2$ and (^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) (^{R}PDI = 2,6-(2',6'-R_2-C_6H_3N=CMe)$_2$$C_5H_3N$; R= iPr, Me) by either the addition of one equivalent of biphenylene or by the addition of one equivalent of *N*,*N*-bis(2-butynyl)tosylamine. The reactivity of (^{iPr}PDI)Fe(biphenyl) and (^{Me}PDI)Fe(biphenyl) (biphenyl = 2,2'-$C_{12}H_8$) was investigated. Addition of hydrogen or silanes resulted in the formation of one molecule of biphenyl and regeneration of the (^{R}PDI)Fe fragment. Treatment of (^{R}PDI)Fe(biphenyl) with excess sulfur resulted in metal complex decomposition, releasing free ligand and dibenzothiophene. Carbon monoxide addition to (^{R}PDI)Fe(biphenyl) caused the formation of a purple diamagnetic intermediate that was identified as having a metal-carbonyl, not the inserted acyl, which eventually released 9-fluorenone and formed (^{R}PDI)Fe(CO)$_2$. The electronic structures of (^{R}PDI)Fe(biphenyl) and (^{R}PDI)Fe(diyne) were elucidated by single crystal X-ray diffraction and zerofield Mössbauer. These complexes are of interest because of the relevant role of a metallocyclic intermediate in the iron-catalyzed, hydrogen-mediated reductive cyclization discussed previously. The electronic structures of both the biphenyl compounds and the diyne complexes were determined to be low spin iron(III) with a monoreduced PDI ligand and a triplet ground state resulting from antiferromagnetic coupling of the PDI ligand and the iron center.

3.2 Introduction

There has recently been a great explosion in the methodologies that are employed for the formation of new carbon-carbon bonds.[1] Primarily these methods use palladium and proceed via a common mechanism, namely oxidative addition followed by transmetallation, and then reductive elimination to form the new carbon-carbon bond.[2] As supplies of palladium and other precious metals dwindle, more available metals will need to be exploited in these types of reactions. Recently, Fürstner and coworkers reported the cross-coupling reaction between Grignard reagents and aryl halides to form new carbon-carbon bonds using low catalyst loadings of the formally iron(-I) compound, $[Li(tmeda)_2Fe(ethylene)_4]$.[3]

One classic substrate used to study oxidative addition of carbon-carbon bonds is biphenylene. This highly strained, anti-aromatic compound has a carbon-carbon bond strength of about 65 kcal/mol and a length of 1.514 angstroms (Figure 3.1). This bond is more than 50 kcal/mol weaker than the single bond in biphenyl and ~35 kcal/mol weaker than typical carbon-carbon single bonds. The weakness of this bond, coupled with the formation of two very strong metal-sp^2C bonds (~71-75 kcal/mol) upon oxidative addition, make this process exothermic by ~80 kcal/mol for electron-rich metal centers.[4]



Bond Distance in Biphenylene

C^1-C^2	1.385 Å
C^2-C^3	1.423 Å
C^3-C^4	1.372 Å
C^4-C^5	1.514 Å
C^5-C^6	1.426 Å

Figure 3.1. Selected bond lengths of crystallographically characterized biphenylene.[5]

Jones has recently communicated the catalytic functionalization of biphenylene with various nucleophiles facilitated by $(Ph_3P)_4Pd$.[6] α-Olefins cleanly react with biphenylene in the presence of *p*-cresol to yield isomeric vinyl-biphenyl derivatives (Figure 3.2). The inferred palladium-metallocycle is never observed but presumably is formed. Mechanistically, from the putative metallocycle the acidic *p*-cresol could first protonate one metal-arene bond, thus enabling olefin insertion into the second metal-arene bond. Subsequent β-hydrogen elimination would account for both observed product isomers. Another reaction method reported by Jones involves the isolation of triaryl species from the palladium-catalyzed, *p*-cresol-mediated cross-coupling of biphenylene and boronic acids (Figure 3.3).

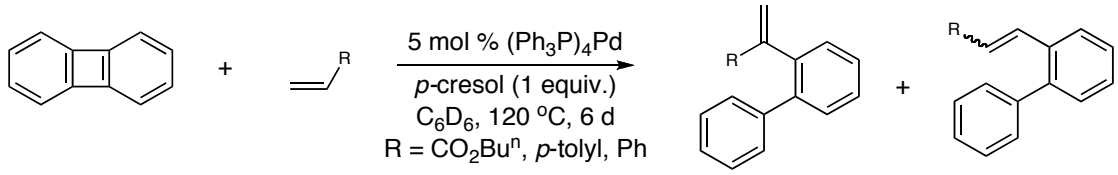


Figure 3.2. Palladium-catalyzed functionalization of biphenylene with a-olefins.

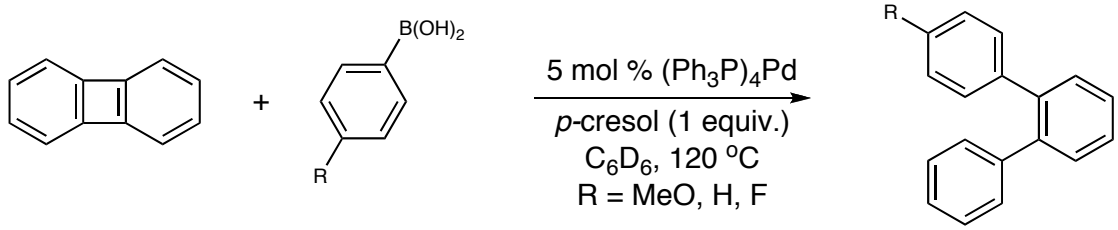


Figure 3.3. Palladium-catalyzed functionalization of biphenylene with boronic acids.

Studies done by Radius and coworkers with $(R^2\text{-NHC})Ni(COD)_2$ (R^2-NHC = 1,3-di(R)imidazole-2-ylidene; $R^2 = Me_2$, $^nPr_2$, Me^iPr, $^iPr_2$)[7] and investigations by Jones using $(^iPr_2PCH_2CH_2NMe_2)Ni(PhCCPh)$ highlight the competency of electron-

rich nickel centers to promote the oxidative addition and subsequent functionalization of biphenylene. An example highlighting this reaction is the synthesis of 9,10-diphenylphenanthrene from biphenylene and diphenylacetylene (Figure 3.4).

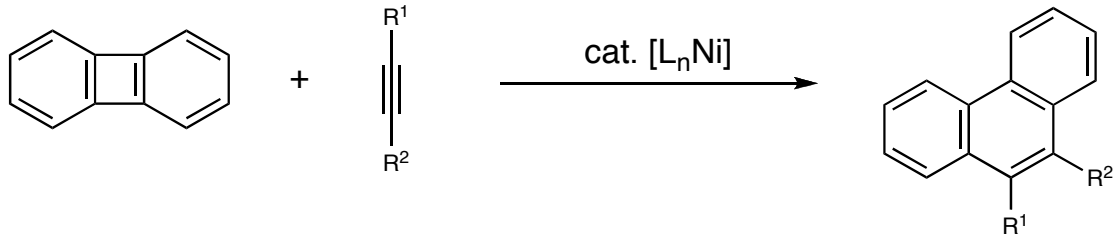


Figure 3.4. Activation of biphenylene by nickel(0) complexes.

The catalytic hydrogenative cyclization of diynes by (^{iPr}PDI)Fe(N_2)$_2$ was reported in chapter one.[8] The proposed intermediate is an iron metallocycle, which should have an analogous structure to the product of biphenylene oxidative addition. Moreover, the presence of the metallocyclic intermediate is supported by the stoichiometric reaction between bis(2-butynyl) tosylamine and (^{iPr}PDI)Fe(N_2)$_2$, which forms the tosylated pyrrolidine via transfer hydrogenation from the isopropyl aryl group of the ligand. It was reported that the diyne cyclization likely proceeds through a ferrous intermediate and that redox changes are confined to the bis(imino)pyridine chelate (Figure 3.5). Despite the evidence for metallocycle formation, its decomposition pathway (sigma bond metathesis with dihydrogen or oxidative addition/reductive elimination of hydrogen) remains unexplored. Elucidating the electronic structure of the intermediate metallocycle via activation of biphenylene may shed more light onto the mechanistic understanding of the hydrogen-mediated iron-catalyzed cyclization of diynes.

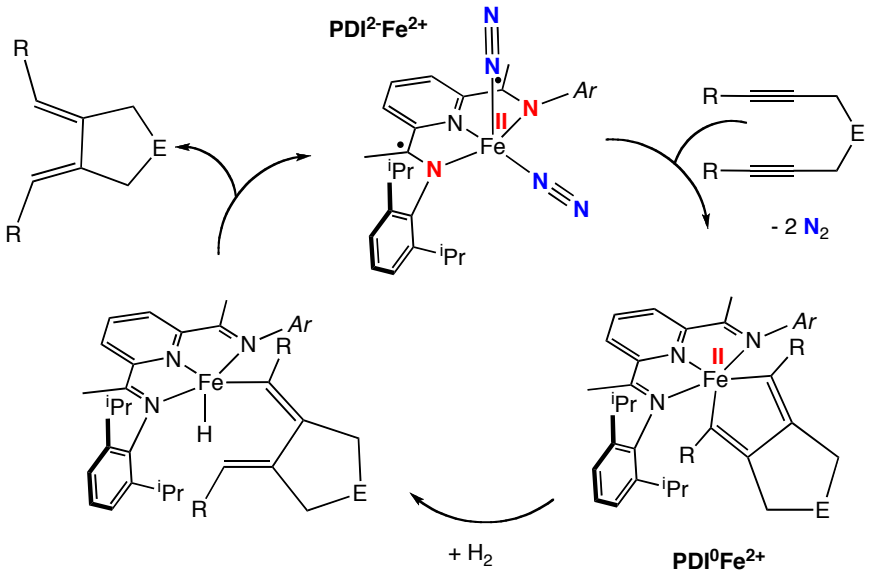


Figure 3.5. Proposed mechanism of diyne reductive cyclization.

This chapter will discuss the oxidative addition of biphenylene to reduced (PDI)Fe compounds. A few facets of the resulting products will be explored. The first is the reactivity of these compounds. Secondly, the electronic structure will be discussed in context of the reactivity. Finally the biphenylene compounds will be compared with the corresponding diyne complexes to see if any similarities in electronic structure can be noted and what effects this may have on the understanding of the mechanism of iron-catalyzed, hydrogen-mediated reductive diyne cyclization.

3.3 Results

Preparation of biphenyl complexes. Treatment of (^{R}PDI)Fe(N_2)$_2$ with one equivalent of biphenylene in ether or benzene allowed for the isolation of (^{R}PDI)Fe(biphenyl) in good to moderate yields after allowing the reaction to stir overnight (Figure 3.6). The purity of the resultant complex was assayed by Mössbauer spectroscopy. The isopropyl compound was isolated in >95 % purity whereas the methyl compound was

initially isolated in about 70 % purity at best. Various attempts were made to prepare this compound more cleanly; however, decomposition ensued the longer the compound was handled. As a result, the subsequent reactions that involved (^{Me}PDI)Fe(biphenyl) were conducted with in situ preparation of the compound. The Mössbauer spectral parameters are listed in Table 3.1, and the plotted data are shown in Figures 3.7 and 3.8.[9]

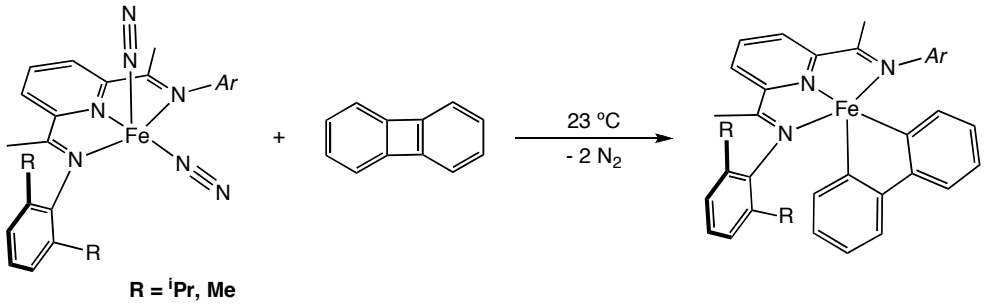


Figure 3.6. Preparation of (^{R}PDI)Fe(biphenyl) compounds.

Table 3.1. Mössbauer spectral data collected at 80 K for (PDI)Fe compounds.

Compound	Isomer Shift, δ (mm/s)	Quadrupole Splitting, ΔE_Q (mm/s)	Gamma, Γ (mm/s)	Percentage of Sample
(^{iPr}PDI)Fe(biphenyl)	0.073	3.54	0.32	>95 %
(^{Me}PDI)Fe(biphenyl)	0.053	3.69	0.32	71 %
(^{iPr}PDI)Fe(diyne)	0.086	3.34	0.29	> 95 %
(^{Me}PDI)Fe(diyne)	0.088	3.10	0.64	86 %

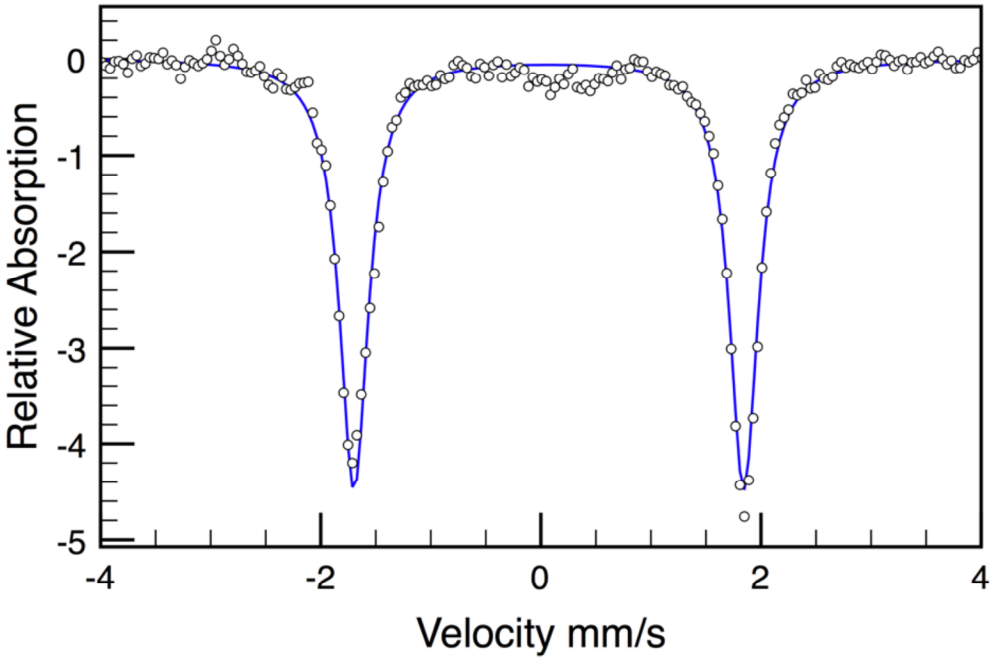


Figure 3.7. Mössbauer spectrum collected at 80 K for (^{iPr}PDI)Fe(biphenyl).

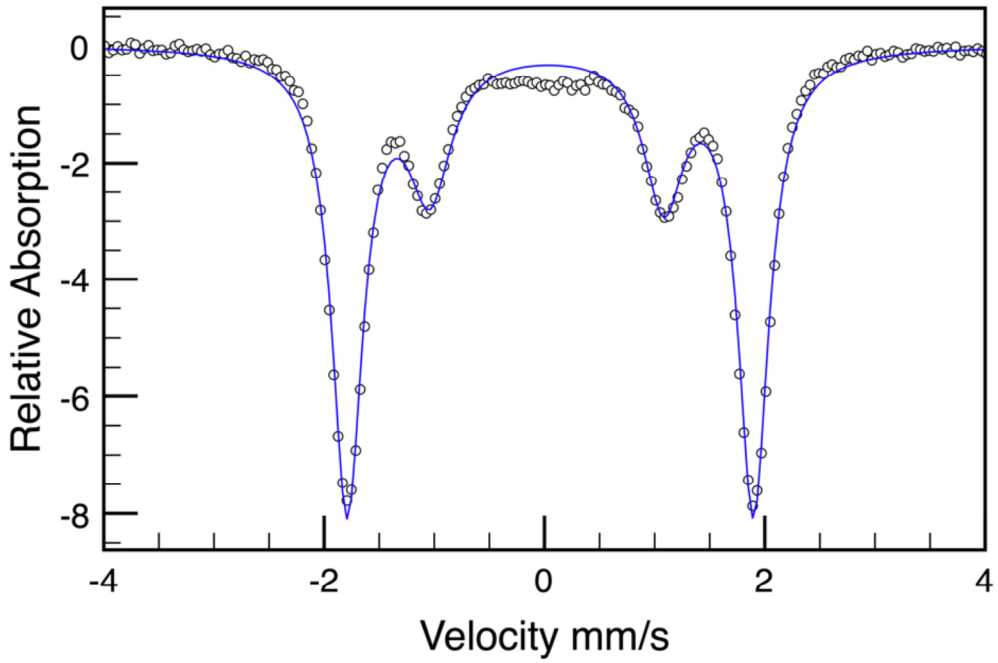


Figure 3.8. Mössbauer spectrum collected at 80 K for (^{Me}PDI)Fe(biphenyl).

(^{iPr}PDI)Fe(biphenyl) was characterized by single crystal X-ray crystallography (Figure 3.9). The complex has nearly idealized square pyramidal geometry with nearly orthogonal angles around the iron center. Reported in Table 3.2 are selected bond lengths and bond angles. The bond distances are consistent with a monoreduced chelate with elongated imine bond lengths of 1.315(4) Å and 1.317(4) Å and contracted carbon$_{imine}$-carbon$_{pyridine}$ lengths of 1.438(4) Å and 1.433(4) Å. Typically, monoreduced ligands have imine bond lengths that range between 1.30 Å and 1.33 Å and carbon$_{imine}$-carbon$_{pyridine}$ bond lengths that range between 1.43 Å and 1.45 Å.[10]

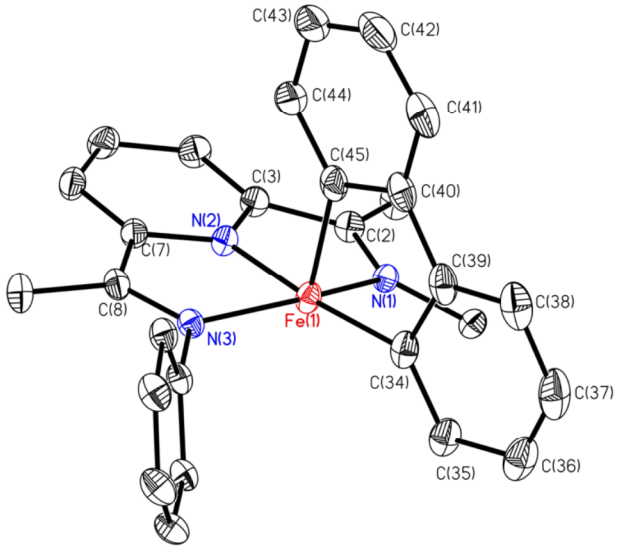


Figure 3.9. Molecular structure of (^{iPr}PDI)Fe(biphenyl) at 30 % probability ellipsoids. Hydrogen atoms, isopropyl groups, and one aniline moeity omitted for clarity.

Table 3.2. Selected bond lengths (Å) and angles (degrees) of (^{iPr}PDI)Fe(biphenyl).

Fe(1)-C(45)	1.943(3)	N(2)-Fe(1)-C(45)	92.47(12)
Fe(1)-N(1)	1.959(2)	N(2)-Fe(1)-N(1)	79.41(9)
Fe(1)-C(34)	1.965(3)	C(45)-Fe(1)-N(1)	99.70(11)
Fe(1)-N(3)	1.988(2)	N(2)-Fe(1)-C(34)	175.09(12)
N(1)-C(2)	1.315(4)	C(45)-Fe(1)-C(34)	84.02(14)
N(3)-C(8)	1.317(4)	N(1)-Fe(1)-C(34)	97.76(10)
C(2)-C(3)	1.438(4)	N(2)-Fe(1)-N(3)	79.46(10)
C(7)-C(8)	1.433(4)	C(45)-Fe(1)-N(3)	94.81(11)
C(39)-C(40)	1.463(5)	C(34)-Fe(1)-N(3)	104.21(11)

Preparation of (^{R}PDI)Fe(diyne) complexes. Diyne complexes were prepared by the treatment of bis(imino)pyridine nitrogen compounds with bis(2-butynyl)tosylamine. These complexes are somewhat unstable and must be isolated quickly to avoid deleterious side reactions (Figure 3.10). (^{iPr}PDI)Fe(biphenyl) undergoes decomposition more slowly than the methyl analog; consequently, it was isolated in higher yield and purity (as measured by Mössbauer spectroscopy). Purity was determined by Mössbauer spectroscopy and it was found that (^{iPr}PDI)Fe(diyne) was >95 % pure where as (^{Me}PDI)Fe(diyne) was only about 86 %. The Mössbauer spectral data is listed in Table 3.1.

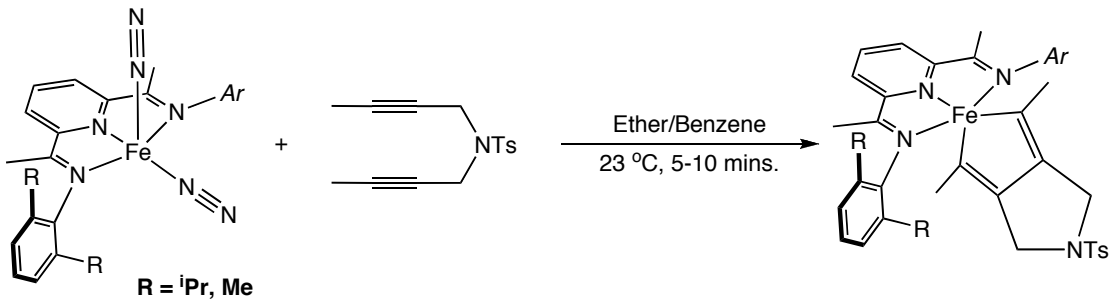
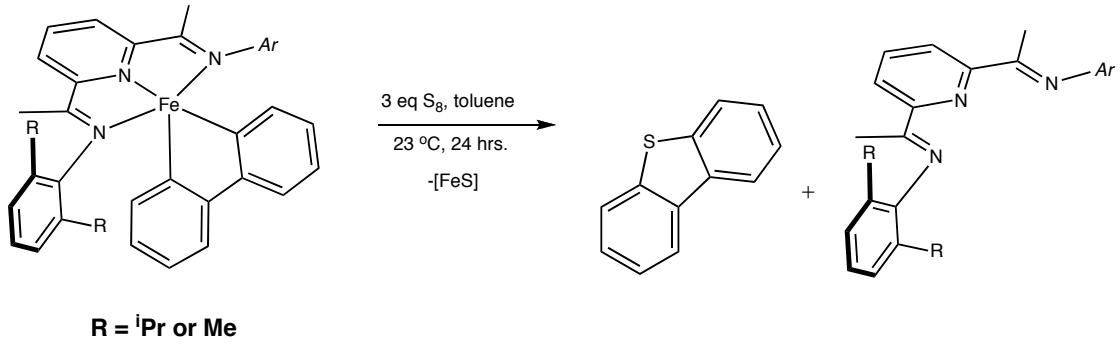


Figure 3.10. Preparation of (^{R}PDI)Fe(diyne) complexes.

Sulfur insertion into biphenyl compounds. When two equivalents of sulfur were added to (^{iPr}PDI)Fe(biphenyl) and the reaction mixture was stirred for 16 hours, the result was a mixture was dibenzothiophene (0.3 equivalents), biphenyl (0.7 equivalents), modified ^{iPr}PDI (0.3 equivalents)[11], and ^{iPr}PDI (0.7 equivalents). When the amount of added sulfur was increased to ~25 equivalents (of sulfur atoms), complete conversion to dibenzothiophene was observed for both the dimethyl ligand and the diisopropyl ligand (Figure 3.11).



R = ^{i}Pr or Me

Figure 3.11. Super stoichiometric sulfur addition to iron-biphenyl compounds.

Hydrogenation of biphenyl compounds. When biphenylene was mixed with (^{iPr}PDI)Fe(N_2)$_2$ or [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2), the solution became bright green and exhibited paramagnetic resonances in the ^{1}H NMR spectrum. Subsequent hydrogen addition resulted in a color change to purple-brown and the paramagnetic resonances disappeared giving way to biphenyl as well as (^{iPr}PDI)Fe(H_2) for the diisopropyl ligand. For the methyl ligand, the resultant ^{1}H NMR spectrum exhibited resonances for biphenyl and a few broad methyl resonances. Similarly, phenylsilane and diphenysilane could also be employed to hydrogenate the biphenyl complexes. However, phenylsilane took forty hours whereas diphenylsilane took in excess of five days (Figure 3.12).

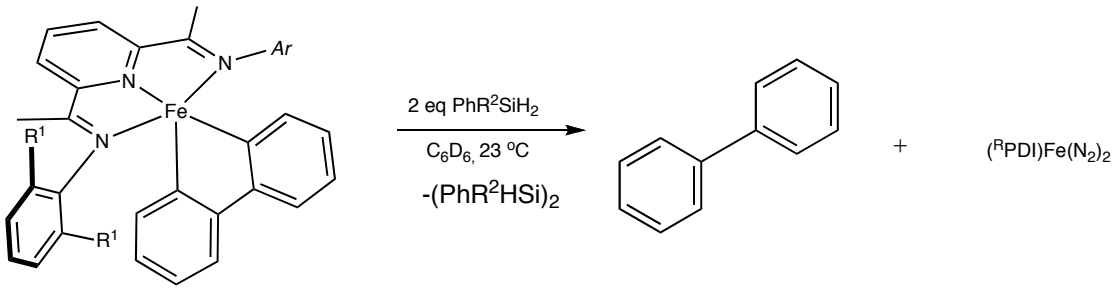


Figure 3.12. Hydrogenation of (^{R}PDI)Fe(biphenyl) using silane as hydrogen source.

Addition of carbon monoxide. Addition of carbon monoxide to (^{iPr}PDI)Fe(biphenyl) resulted in the formation of a transient diamagnetic purple product. This diamagnetic species gave way to a brown solution which eventually formed (^{iPr}PDI)Fe(CO)$_2$ and 9-fluoroenone. Similar behavior was observed for (^{Me}PDI)Fe(biphenyl).

Transfer hydrogenation reactions. When (^{iPr}PDI)Fe(biphenyl) was allowed to stand in benzene-d_6 for forty hours, the green solution turned brown and the paramagnetic resonances dissipated in the ^{1}H NMR spectrum. Biphenyl was observed in the ^{1}H NMR spectrum. Subsequent hydrolysis of the reaction mixture allowed for identification of the dehydrogenated ligand. When this reaction was repeated with the deuterated iron compound, (^{iPr}PDI*)Fe(biphenyl) (^{iPr}PDI* = d_{24}), the reaction required four days to reach completion. After aqueous degradation, the products were identified as d_1-biphenyl and dehydrogenated ^{iPr}PDI*-d_{23} (Figure 3.13).

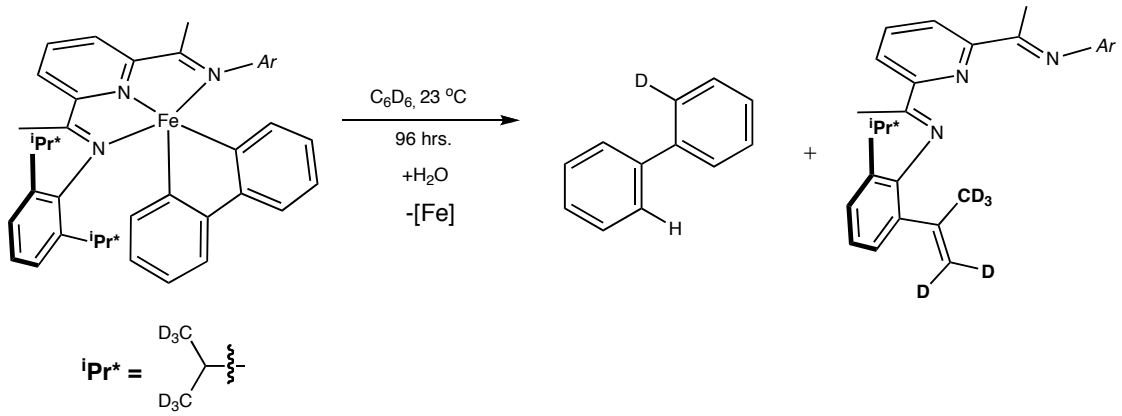


Figure 3.13. Transfer hydrogenation reaction of labeled (^{iPr*}PDI)Fe(biphenyl).

3.4 Discussion

The activation of biphenylene by group 10 transition metals has been well established, as described above. The subsequent chemistry that these metallocyclic intermediates can undergo has found some utility. Not surprisingly, (^{iPr}PDI)Fe(N_2)$_2$, which is isolobal with the bis(phosphine)nickel fragment, also has the ability to activate the weak carbon-carbon bond of biphenylene.

The elongated imine bond lengths (~1.32 Å) and shortened carbon$_{imine}$-carbon$_{pyridine}$ bond lengths (~1.44 Å) of (^{R}PDI)Fe(biphenyl) indicate that the ligand is monoreduced (PDI^{-1}). The low isomer shift (~0.07 mm/s) of (^{iPr}PDI)Fe(biphenyl) implicates low spin iron(III). The same electronic structure is used to describe bis(imino)pyridyl iron alkyl imides, (^{R}PDI)Fe(NR^2) (R^2 = ^{Cy}Oct, 1-Ad, ^{i}Pr), which also exhibit low isomer shifts (d ~ 0 mm/s). The spin states and oxidation states of the iron-imides have been further corroborated by pre-edge analysis (K-edge spectroscopy) and by theoretical calculations which indicate iron(III).[12] Moreover, the strength of the ligand field also contributes to the low spin nature of the biphenyl compound; this differs from other (PDI)Fe(dialkyls) which are high spin iron(III).[13] Since phenyl is a stronger field ligand than alkyl, the increased orbital splitting is not

unexpected. The measured moment of 2.8 μ_B is consistent with an S=1 ground state, implying that there is a set of unpaired spins with one electron on the ligand and the other in a metal orbital. With a triplet ground state, intermediate iron(III) is a plausible electronic structure description; however the small isomer shift makes this argument more dubious as other examples of intermediate spin iron(III) compounds, the bis(imino)pyridyl iron aryl imides, (^{R}PDI)Fe(NAr) (Ar = 2,6-^{i}Pr$_2$-C$_6$H$_3$, 2,6-Et$_2$-C$_6$H$_3$, 2,5-^{t}Bu$_2$-C$_6$H$_3$, 2,4,6-Me$_3$-C$_6$H$_3$), have higher isomer shifts around 0.3 mm/s. Thus, (^{iPr}PDI)Fe(biphenyl) is best described as a low spin iron(III) compound with a triplet ground state and a monoreduced ^{iPr}PDI ligand.

Ultimately magnetic Mössbauer will be used to determine the sign of the quadrupole splitting, which aids in determining the electric field gradient and hence orbital occupancy. However, a qualitative molecular orbital diagram can be suggested based on the previous data and is presented in Figure 3.14. Low spin iron(III) is suggested because of the small isomer shift. The large quadrupole splitting suggests that the electron density around the nucleus is concentrated in either the xy plane or along the z-axis. The molecular orbital diagram is consistent with a charge that is spread along the z-axis. The unpaired spins that do not couple on the ligand and on the iron center are consistent with the molecular orbital diagram because PDI π^* is of the wrong symmetry to interact with d_z^2, a fact which explains the triplet ground state.

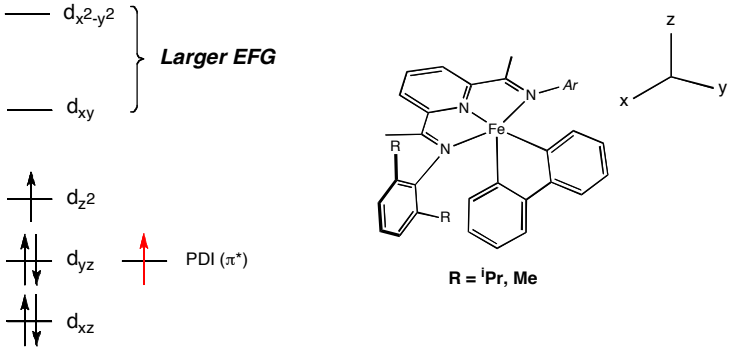


Figure 3.14. Proposed electronic structure of (^{R}PDI)Fe(biphenyl).

The reactivity of (^{R}PDI)Fe(biphenyl) is somewhat limited to only a few simple metal-mediated insertion reactions. Interestingly, the insertion of carbon monoxide proceeds through a metal-carbonyl, which was observed by ^{1}H and ^{13}C NMR. The metal carbonyl is probably the intermediate because the ^{13}C chemical shift (~210 ppm) is more consistent with a metal carbonyl rather than a metal-acyl. Barring the requirement of imine dissociation for CO coordination, this intermediate is one of the few six-coordinate (PDI)Fe species that has been observed experimentally.

Oxidative addition of carbon-halogen bonds and carbon-oxygen bonds to (^{iPr}PDI)Fe(N_2)$_2$ has been documented. For alkyl halides, oxidative addition occurs at one metal center to form the intermediate five-coordinate complex. Next follows ejection of alkyl radical, which is subsequently trapped by another equivalent of (^{iPr}PDI)Fe(N_2)$_2$, thus requiring two metal centers to consume one equivalent of alkyl halide. The electronic structure of the resulting products from oxidative addition can be described as iron(II) with a mono-reduced ligand. However, there is one example where the oxidative addition product has been observed and isolated. The oxidative addition of vinyl acetate cleanly results in the formation of (^{iPr}PDI)Fe(OAc)(vinyl), which presumably possesses no mechanism by which radical ejection or β-hydrogen elimination can occur. The product of this oxidative addition can be described as low

spin iron(III) with a mono-reduced PDI ligand. Similarly, the only other known example of clean oxidative addition to (^{iPr}PDI)Fe fragment is biphenylene. Both of these complexes have the same electronic structure, with oxidation at the metal center and reduction at the ligand, thus enabling the two-electron oxidative addition to occur.[14]

(^{R}PDI)Fe(biphenyl) complexes have the same electronic structure as the proposed metallocycle for the hydrogen-mediated reductive cyclization of diynes catalyzed by (^{iPr}PDI)Fe(N_2)$_2$. Despite the short lifetime of the intermediate of the hydrogenative cyclization of diynes, Mössbauer spectra of these complexes were collected. If the intermediate could be isolated in under 30 minutes, the product was observed to be at least 90 % pure. For (^{iPr}PDI)Fe(diyne), the isomer shift was measured to be 0.086 mm/s and for (^{Me}PDI)Fe(diyne), the isomer shift was measured to be 0.088 mm/s. These two values are essentially equivalent to each other and similar to the values that were measured for the biphenyl compounds. This is highly suggestive of a similar electronic structure to the biphenyl compound. Thus, it is more accurate to describe the first step of the diyne cyclization (formation of a metallobicycle) as an oxidation of the metal and reduction of the ligand (Figure 3.15). This is different than the previously suggested mechanism, which contended that the ferrous oxidation state is maintained throughout the entire reaction sequence and that the ligand is responsible for the two-electron processes that occur during the reaction. In light of this evidence, the means by which the hydrogen adds to the metallocyclic intermediate is still not definitive. Either a sigma bond methathesis or oxidative addition of H_2 followed by reductive elimination may be operative. Since no alkenyl hydrides have ever been prepared in our group, further study of that intermediate seems unlikely; however, the intermediate is likely iron(III) since (^{R}PDI)Fe(alkyl)$_2$ and (^{R}PDI)Fe(biphenyl) complexes are comparable.

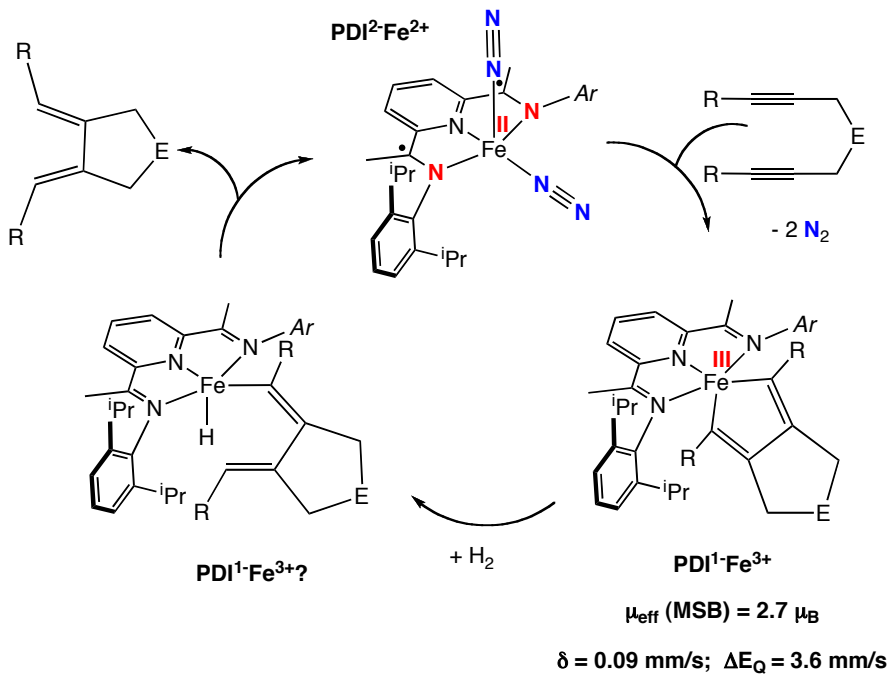


Figure 3.15. Modified catalytic cycle of iron-catalyzed reductive cyclization of diynes.

3.5 Conclusion

Understanding the electronic structure of intermediates in a catalytic cycle is vital if optimization and mechanistic understanding are desired. In this chapter, insight into the hydrogen-mediated iron-catalyzed cyclization was gained by studying a series of (^{R}PDI)Fe(biphenyl) compounds. Characterization by single crystal X-ray crystallography and Mössbauer spectroscopy indicates that iron biphenyl compounds are low spin iron(III) complexes that have a triplet ground state and monoreduced PDI ligand. (^{R}PDI)Fe(biphenyl) compounds undergo stoichiometric insertion reactions with carbon monoxide and sulfur. Moreover, these complexes react with hydrogen sources to form biphenyl. Iron-catalyzed hydrogen-mediated reductive cyclizations proceed through an intermediate with the same electronic structure as (^{iPr}PDI)Fe(biphenyl). These low spin iron(III) metallocyclic intermediates form by

oxidation of the metal center and reduction of the ligand when diynes are added to (^{iPr}PDI)Fe(N_2)$_2$. This observation indicates that the redox activity of PDI in this system is not as simple as was previously thought. The former hypothesis suggested that the PDIFe framework allows for the shuttling of two electrons from the ligand to the substrate, which maintains the ferrous oxidation state at the metal center. Despite the development of a better understanding of the first intermediate of the catalytic cyclization of diynes, the mechanism or the species responsible for the addition of hydrogen across the iron-alkenyl bonds remains unclear: two possibilities are sigma-bond methathesis or oxidative addition followed by reductive elimination.

3.6 Experimental Procedures

General Considerations. All air- and moisture-sensitive manipulations were carried out using standard vacuum line, Schlenk and cannula techniques or in an MBraun inert atmosphere drybox containing an atmosphere of purified nitrogen. The MBraun drybox was equipped with a cold well designed for freezing samples in liquid nitrogen. Solvents for air- and moisture-sensitive manipulations were initially dried and deoxygenated using literature procedures.[15] Argon and dihydrogen gas were purchased from Airgas Incorporated and passed through a column containing manganese oxide supported on vermiculite and 4 Å molecular sieves before admission to the high vacuum line. Benzene-d_6 was purchased from Cambridge Isotope Laboratories and distilled from sodium metal under an atmosphere of argon and stored over 4 Å molecular sieves or sodium metal. $CDCl_3$ was purchased from Cambridge Isotope Laboratories and used as received or distilled from calcium hydride.

^{1}H NMR spectra were recorded on Varian Mercury 300, Inova 400 and 500 spectrometers operating at 299.763, 399.780 and 500.62 MHz, respectively. All chemical shifts are reported relative to $SiMe_4$ using ^{1}H (residual) chemical shifts of the

solvent as a secondary standard. For paramagnetic molecules, the ^{1}H NMR data are reported with the chemical shift followed by the peak width at half height in Hertz or multiplicity, followed by integration value and where possible, peak assignment.

Mass spectra were acquired using a JEOL GCMate II mass spectrometer operating at 500 (LRMS) or 3000 (HRMS) resolving power (20% FWHM) in positive ion mode and an electron ionization (EI) potential of 70 eV. Samples were introduced via a GC inlet using an Agilent HP 6890N GC equipped with a 30 m (0.25 μ i.d.) HP-5ms capillary GC column. The carrier gas is helium with a flow rate of 1 mL/min. Samples were introduced into the GC using a split/splitless injector at 230 ºC with a split ratio of 10:1 (HRMS) or 50:1 (LRMS). The bis(imino)pyridine iron dinitrogen compounds, (^{iPr}PDI)Fe$(N_2)_2$[16] and (^{Me}PDI)Fe$(N_2)]_2$-μ-(N_2)[17] were prepared according to literature procedures.

Preparation of Biphenylene. Biphenyl (10.0 g, 64.9 mmol) was suspended in 25 mL of dry N,N,N',N'-tetramethylethylenediamine in a 250-mL round bottom flask under an atmosphere of argon. A solution of *n*-butyl lithium (100 mL, 1.4 M, 140 mmol) in hexanes was added dropwise to the suspension and stirred for 3 days at room temperature. During this time the reaction turned from light yellow to dark red. After three days approximately 200 mL of pentane was added to the reaction mixture and it was filtered under argon. The solid was collected and dried to yield 14.8 g of a dark yellow powder (57.6 % yield) identified as the expected dilithio salt of biphenylene. This product (7.56 g, 19.0 mmol) and dry zinc dichloride (6.17 g, 45.4 mmol) were charged into a 250 mL round bottom flask. Approximately 25 mL of dry THF (125 mL) were added by vacuum transfer to the mixture at -78 ºC. The reaction mixture was warmed to room temperature and stirred for three hour under argon. Dry copper (II) chloride (6.17 g, 45.8 mmol) was then added and the reaction was stirred again at -

78 ºC for two hours. Aqueous HCl (45 mL, 4 M) was added to the reaction mixture, which was then extracted with toluene (3 x, 80 mL). The combined organic layers were washed with water (2x, 50 mL), then brine (25 mL), and dried over sodium sulfate. The drying reagent was removed via filtration and the solvent was removed under reduced pressure to yield 1.45 g of a brown solid. The brown solid was recrystallized was hot cyclohexane to yield 0.940 g (33 %) of yellow needles identified as biphenylene. Spectral properties were consistent with previous reported results.[18]

Preparation of *N*,*N*-Di(but-2-ynyl)-4-methylbenzenesulfonamide. A 100 mL round bottom flask was charged with 4.00 g (29.0 mmol) of potassium carbonate, approximately 40 mL of dimethylformamide and 1.15 g (6.70 mmol) of 4-methylbenzenesulfonamide. The resulting suspension was stirred for one hour at room temperature. After this time, 2.12 g (14.5 mmol) of but-2-ynyl-1-methanesulfonate were added dropwise and the reaction mixture was stirred at room temperature for 26 hours. Approximately 200 mL of water was then added and the desired product extracted with 400 mL of toluene. The combined organic layers were successively washed with water (3x, 50 mL), and then dried over magnesium sulfate. Evaporation of the toluene yielded a yellow solid. The yellow solid was dissolved in diethyl ether, passed through dry neutral alumina, and concentrated to yield 0.950 g (52 %) of a white powder. Spectral properties are consistent with previously reported data.[19]

Preparation of (^{iPr}PDI)Fe(biphenyl). Biphenylene (0.061 g, 0.40 mmol) was added to a 20 mL of solution containing 0.232 g of (^{iPr}PDI)Fe(N_2)$_2$ (0.39 mmol) in pentane. The reaction was stirred for 14 hours after which time a green precipitate formed. The solid (0.110 g, 0.16 mmol) was collected by filtration. The supernatant was reduced to

approximately half the original volume and stored at -35 ºC and yielded an additional 0.059 g (0.086 mmol) of a green powder. The combined mass of the isolated green solid was 0.169 g (62 % yield) and was identified as (^{iPr}PDI)Fe(biphenyl). X-ray diffraction-quality crystals were grown from diethyl ether/pentane at -35 ºC. Anal. Calcd for $C_{45}H_{51}FeN_3$: C, 78.36; H, 7.45; N, 6.09. Found: C, 77.92; H, 7.28; N, 6.00. Magnetic susceptibility balance (23 ºC): $\mu_{eff} = 2.8\ \mu_B$.

Preparation of (^{Me}PDI)Fe(biphenyl). Biphenylene (39 mg, 0.26 mmol) was dissolved in approximately 2 mL of diethyl ether. The diethyl ether solution was added to a solution of [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) (0.118 g, 0.13 mmol dimer) in approximately 9 mL of diethyl ether. The reaction mixture was stirred for 8 hours and a color change from red-brown to dark green was observed. The solvent was removed in vacuo and the resulting residue was dissolved in a minimal amount of toluene. The dark green solution was filtered through a pad of Celite and toluene was removed under reduced pressure. The residue was recrystallized from diethyl ether to yield 83 mg (0.14 mmol, 56 % yield) of a green crystalline solid which is about 75% pure as determined by Mössbauer.

Preparation of (^{iPr}PDI)Fe(diyne). A scintillation vial was charged with 75 mg (0.126 mmol) of (^{iPr}PDI)Fe(N_2)$_2$ and approximately 5 mL of pentane. A solution of *N,N*-bis(buty-2-ynl)tosylamine (36 mg, 0.130 mmol) was prepared in 1 mL of toluene. The solution of the diyne was added dropwise to the pentane solution containing the iron compound. Bubbling was observed immediately following the addition. The solution turned dark purple and eventually a dark green-purple precipitated formed, which was collected by filtration and washed with pentane. The purple solid was isolated, dried

and collected yielding 75 mg (73%) of (^{iPr}PDI)Fe(diyne). Magnetic susceptibility balance (23 ºC): $\mu_{eff} = 2.8\ \mu_B$.

Preparation of (^{Me}PDI)Fe(diyne). A scintillation vial was charged with 60 mg (0.064 mmol dimer) of [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) and approximately 4 mL of benzene resulting in a reddish-brown solution. A solution of *N,N*-bis(buty-2-ynl)tosylamine (36 mg, 0.130 mmol) was prepared in 1 mL of benzene. The solution of the diyne was added dropwise to the benzene solution containing the iron compound. Bubbling was observed immediately following the addition. The solution turned green after five minutes. The reaction was frozen and the benzene was removed by sublimation under vacuum. The residue was then washed with cold ether and dried under vacuum to yield 95 mg of a dark green solid. The product was analyzed by Mössbauer spectroscopy and was determined to be 84 % pure, the likely contaminated by a mono-X species (most likely (^{Me}PDI)FeBr).

Stoichiometric Reactions

Addition of S_8 to (^{R}PDI)Fe(biphenyl) Compounds. A 20-mL scintillation vial was charged with 0.051 mmol of (^{iPr}PDI)Fe(piphenyl) or [(^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) and biphenylene and approximately 5.0 mL of toluene. Elemental sulfur (0.156 mmol S_8, 25 equiv. sulfur) was added to the dark green solution. The reaction mixture was stirred at room temperature for 16 hours and a color change to dark brown was observed. Filtration of the toluene solution through a pad of Celite and concentration of the toluene solution under vacuum resulted in isolation of dibenzothiophene and free bisligand. The identity of dibenzothiophene was confirmed by comparison of the ^{1}H NMR spectrum to an authentic sample.

Hydrogenation of (^{R}PDI)Fe(biphenyl) Compounds. A J. Young NMR tube was charged with 0.029 mmol of (^{iPr}PDI)Fe(biphenyl) or (^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) and biphenylene and approximately 0.650 mL of benzene-d_6 were added. The tube was degassed and 4 atm of hydrogen was added. Upon thawing, a color change from dark green to red-brown was observed. Analysis by ^{1}H NMR spectroscopy revealed the formation of biphenyl and (^{R}PDI)Fe(H_2).[16] When D_2 was used, incorporation of deuterium was observed at the 2 and 2' positions on the biphenyl ring.

Reaction of (^{R}PDI)Fe(biphenyl) with Silanes. A J. Young NMR tube was charged with 0.029 mmol of (^{iPr}PDI)Fe(piphenyl) or (^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) and biphenylene and approximately 0.650 mL of benzene-d_6 were added. The desired silane (0.058 mmol) was added and the solution was allowed to stand at room temperature. In the case of $PhSiH_3$, the reaction was complete in under 40 hours. Diphenyl silane required extended reaction times of 80 hours.

Transfer Hydrogenation from (^{iPr}PDI)Fe(biphenyl). A solution of (^{iPr}PDI)Fe(biphenyl) (10 mg, 0.015 mmol), in benzene-d_6 (0.50 mL) was prepared in a J. Young tube. After sitting at room temperature for about 40 hours, the green solution turned brown and all of the paramagnetic resonances in the ^{1}H NMR disappeared. Aqueous degradation of the reaction mixture resulted in the observation of one equivalent of free ligand (^{iPr}PDI) and one equivalent of biphenyl.

Addition of Carbon Monoxide to Iron-Biphenyl Compounds. A J. Young NMR tube was charged with 0.029 mmol of (^{iPr}PDI)Fe(piphenyl) or (^{Me}PDI)Fe(N_2)]$_2$-μ-(N_2) and 0.650 mL of benzene-d_6 were added. The NMR tube was degassed on the high vacuum line and 1 atm of CO was added. Upon thawing, a color change from dark

green to purple was observed. At longer times, a color change to red-brown then finally to green was observed. The purple solution contained a product that had a ^{13}C-NMR chemical shift at 220 ppm indicating a carbonyl, not an acyl. 9-Fluorenone was identified as a byproduct of the reaction by comparison to authentic sample.

Catalytic Reactions

Catalytic Hydrogenation of Biphenylene (H_2 Source). A 3 mL solution containing 0.030 mg (0.197 mmol) of biphenylene in toluene was prepared and 5 mol % of the desired iron compound was added. The thick walled glass bomb was degassed on the vacuum line and 4 atm of H_2 was added. For $[(^{Me}PDIFe(N_2)]_2$-μ-(N_2), only 40 % conversion was observed after 8 hours when the reaction was run at room temperature. However, when the reaction was run at 65 ^oC, complete consumption of biphenyl was observed with isolation of biphenyl (according to ^1H NMR). For $^{iPr}PDIFe(N_2)_2$, the reaction only converted 25 % of the biphenylene to biphenyl after 8 hours when run at room temperature. However increasing the reaction temperature resulted in 41 % conversion of biphenyl to biphenylene.

Catalytic Hydrogenation of Biphenylene ($PhSiH_3$ Source). Biphenylene (30 mg, 0.197 mmol) was combined with 43 mg phenylsilane (0.395 mmol) in 3 mL of toluene in the presence of an iron catalyst (5 mol %). The expected product biphenyl was observed by ^1H NMR as was the dehydrogenated phenyl silane dimmer. The reactions were monitored by ^1H NMR and integrating biphenyl to biphenylene resonances. In the case of $[^{Me}PDIFe(N_2)]_2$-μ-(N_2), 49 % conversion was observed after 48 hours and stirring the reaction for 5 days did not facilitate any further reaction. In the case of $^{iPr}PDIFe(N_2)_2$, after 48 hours, only 11 % conversion was observed and further reaction for 5 days showed no increase in the yield.

Mössbauer Spectroscopy

Mössbauer Spectrometer Specifications. Zero-field ^{57}Fe Mössbauer spectra were recorded on a SEE Co. Mössbauer spectrometer (MS4) at 80 K in constant acceleration mode. ^{57}Co/Rh was used as the radiation source. WMOSS software was used for the quantitative evaluation of the spectral parameters (least-squares fitting to Lorentzian peaks). The minimum experimental line widths were 0.23 mm/s. Good quality data when fit has line widths that are less than 0.4 mm/s. The temperature of the sample was controlled by a Janis Research Co. CCS-850 He/N2 cryostat within an accuracy of 0.3 K. Isomer shifts were determined relative to a-iron at 298 K.

Table 3.3. Mössbauer spectral data collected at 80 K for (PDI)Fe compounds.

Compound	Isomer Shift, δ (mm/s)	Quadrupole Splitting, ΔE_Q (mm/s)	Gamma, Γ (mm/s)	Percentage of Sample
(^{iPr}PDI)Fe(biphenyl)	0.073	3.54	0.32	>95 %
(^{Me}PDI)Fe(biphenyl)	0.053	3.69	0.32	71 %
Minor component	0.020	2.12	0.47, 0.43	29 %
(^{iPr}PDI)Fe(diyne)	0.086	3.34	0.29	> 95 %
(^{Me}PDI)Fe(diyne)	0.088	3.10	0.64	86 %
Minor component	0.66	1.32	0.74, 0.54	14 %

Procedure for Collecting Mössbauer Spectra. The sample was placed into the sample holder in a dry box. Upon completion of sample prep, the holder was immersed in liquid nitrogen. The sample holder was attached to the rod while submerged in liquid nitrogen. Prior to placing rod with sample in the machine, the chamber was evacuated under dynamic vacuum. After the rod was securely placed into the instrument, the chamber was filled with helium. Data collection began when the internal temperature of the sample chamber was about 80 K.

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